Diagnosis and Management of Aspergillus Diseases: Executive Summary of the 2017 ESCMID-ECMM-ERS Guideline

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Abstract

The European Society for Clinical Microbiology and Infectious Diseases, the European Confederation of Medical Mycology and the European Respiratory Society Joint Clinical Guidelines focus on diagnosis and management of aspergillosis. Of the numerous recommendations a few are summarized here. Chest computed tomography as well as bronchoscopy with bronchoalveolar lavage (BAL) in patients with suspicion of pulmonary invasive aspergillosis (IA) are strongly recommended. For diagnosis, direct microscopy preferably using optical brighteners, histopathology and culture are strongly recommended. Serum and BAL galactomannan is recommended as markers for the diagnosis of IA. PCR should be considered in conjunction with other diagnostic tests. Pathogen identification to species complex level is strongly recommended for all clinically relevant *Aspergillus* isolates; antifungal susceptibility testing should be done in patients with invasive disease in regions with resistance found in contemporary surveillance programmes. Isavuconazole and voriconazole are the preferred agents for first line treatment of pulmonary IA, while liposomal amphotericin B is moderately supported. Combinations of antifungals as primary treatment options are not recommended. TDM is strongly recommended for patients receiving posaconazole suspension or any form of voriconazole for IA treatment, and in refractory disease, where a personalized approach considering reversal of predisposing factors, switching drug class and surgical intervention is also strongly recommended. Primary prophylaxis with posaconazole is strongly recommended in patients with acute myelogenous leukaemia or myelodysplastic syndrome receiving induction chemotherapy. Secondary prophylaxis is strongly recommended in high-risk patients. We strongly recommend treatment duration based on clinical improvement, degree of immunosuppression and response on imaging.

Introduction

This is the third fungal diagnosis and management clinical guideline published in cooperation with various European scientific societies [1-9]. This part of the guideline regarding invasive and chronic aspergillosis is a condensation of all the recommendations made by the guideline subcommittees and presented in tables for easier and faster reading. More details on how the recommendations were arrived at are planned in supplementary publications. This *Aspergillus* guideline will follow the style of other guidelines by including diagnostic and therapeutic guidance. Other scientific groups have published guidelines on this topic previously and all follow the common goal to provide clinicians with best guidance in their everyday working environment. Our goal was to provide a comprehensive European guideline focusing on the life-threatening diseases caused by *Aspergillus* spp.

Methods

Author panel recruitment and organisation was similar to what was done previously [10]. In brief, experts in the field were nominated by the three societies ESCMID, ECMM, and ERS. The total 53 authors were grouped into their special fields of expertise. Subgroup coordinators were responsible for the first draft of recommendations. There were two face-to-face meetings followed by numerous electronic exchanges. Some of the first recommendations were presented at ECCMID 2014. This summary was reviewed and approved by all authors and sent to the ESCMID guideline director for public review. Then the final version was submitted to Clinical Microbiology and Infection for additional peer review and subsequent publication. Only the rationale of the chronic pulmonary aspergillosis (CPA) guideline was published ahead of time [11].

Questions were predefined and modified where appropriate and the strength of recommendation and quality of evidence was slightly modified (Table 1) [12]. Diagnostic tests are regarded as interventions.

Summary of Recommendations

Diagnostic Procedures

Early diagnosis of invasive aspergillosis (IA) is a challenge and should be based on the integration of clinical, radiological and microbiological data.

Thoracic Imaging

In patients at risk for IA with fever of unknown origin or clinical symptoms of lower respiratory tract infection who remain febrile despite broad-spectrum antibacterial treatment, thin-section chest computed tomography (multidetector (MDCT), multislice (MSCT), spiral CT, high resolution CT) at optimized dose (according to ALARA "As Low As Reasonably Achievable" principle) is the imaging modality of choice **(AII)** [13-23]. Pulmonary CT angiography may be of interest in the early diagnosis of IA by depicting directly vessel occlusion at the level of a suspicious fungal lesion with a potential high negative predictive value regarding imaging evaluation [24-26], and is required in case of haemoptysis **(AII).** In selected patients where CT is not wanted or feasible, MRI of the lungs may represent an alternative imaging to thin-section MSCT [27-32], PET-CT being of modest interest in the diagnostics of IA [33, 34].

No CT scanning technique is 100% sensitive or specific for pulmonary IA [35-37]: Classical CT findings of angioinvasive aspergillosis include macronodule(s) >1 cm, which may be surrounded by a halo of ground-glass attenuation (halo sign, early phase, inconstant) [36, 38-40], pleural based wedge-shaped areas of consolidation [41], alveolar consolidations [36, 42, 43], masses (especially in SOT recipients) [15, 38], internal low attenuation[44], reverse halo sign [45], cavity or air-crescent sign (delayed finding), ground glass opacities and pleural effusion [17, 35, 46]. Bronchoinvasive forms may appear as tracheal or bronchial wall thickening, centrilobular nodules with tree in bud appearance [14] in a patchy distribution, predominant peribronchial areas of consolidation [47] or bronchopneumonia [46] (Table 2).

Bronchoalveolar Lavage and Biopsies

Other diagnostic procedures include early bronchoalveolar lavage (BAL) **(AII)** [48-54], guided by CT-findings [55, 56], and less frequently CT-guided transthoracic biopsies, video-assisted thoracoscopic surgery (VATS), open lung biopsies, transbronchial biopsies or convex endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA), the latter technique appearing to be a promising procedure in this setting [28, 57-72]. Contraindications to these techniques need to be considered.

Imaging of other Sites

Moreover, according to clinical symptoms, paranasal CT, CT or MRI of the CNS as well as abdominal CT may also be required. In particular, findings of sinusitis with bone erosion may be observed, intracranial and/or intraorbital extension of the disease being best evaluated by MRI [73-75]. In the brain, due to direct spread from paranasal sinuses or haematogenous dissemination, meningeal enhancement or empyema, cerebral abscess, mycotic aneurysms as well as haemorrhagic lesions and rarely stroke may be seen [76-79].

Microscopy and Culture

Both microscopy and culture should be attempted on appropriate specimens from patients at risk for IA **(AII)** with a priority for culture in most cases where insufficient material is available**.** Demonstrating tissue invasion by hyphae through microscopic examination of biopsy or autopsy material provides a diagnosis of proven invasive fungal infection. However, the sensitivity of microscopy for IA is 50% at best [80]. Specimens may be examined as a wet mount preparation with or without the addition of 10% potassium hydroxide. Fluorescent dyes such as Calcofluor White™ or Blancophor™ have the advantages of increased sensitivity, rapid turnaround time, and broad applicability but are not specific for *Aspergillus* **(AII).** Gomori's methenamine silver stain (GMS) and periodic acid-Schiff (PAS) can be applied to histological sections and smears and should be conducted in all cases in which IA is considered a possibility (Table 3). Respiratory secretions from patients with suspected aspergillosis must be processed rapidly for culture to prevent overgrowth by bacteria and yeasts. To achieve

241 optimal recovery of *Aspergillus* from BAL fluid, centrifugation of the sample is advised with
242 investigation of the sediment **(AIII).** It is recommended that cultures of high volume untreated sputum
243 and BAL should be performed as opposed to culturing small volumes of digested, liquefied samples
244 [81] (Table 4). Specific media to support fungal growth are recommended. Species identification to the
245 complex level should be done for clinically relevant isolates from patients who need antifungal
246 treatment, and for epidemiological purposes (AIII) (Table 5).
247
248 **Non-Culture Based Assays**
249 Galactomannan (GM) detection in fluids (especially BAL) is more sensitive than culture for diagnosis of
250 IA. GM is reported as optical density index (ODI). In serum samples an ODI cut-off of 0.5 results in high
251 sensitivity in haematological patients in the absence of mould-active prophylaxis **(AI)** (Table 6). Serial
252 screening for serum GM in prolonged neutropenia and in allogeneic stem cell transplantation
253 recipients during the early engraftment phase has a high sensitivity and negative predictive value (NPV)
254 for IA **(AII)** [82]. Serial screening is not recommended in patients on mould-active prophylaxis [83].
255 Sensitivity of serum GM testing is significantly lower in non-neutropenic versus neutropenic patients
256 [84]. Decrease of the ODI during the first two weeks of antifungal therapy is a reliable predictor of a
257 satisfactory response in cancer patients [85]. GM detection in BAL specimens has an excellent
258 performance with evidence that ODI of 0.5–1.0 has decreased predictive values compared with results
259 of >1.0 [86] **(AII)** (Table 7). The test also has diagnostic value in patients undergoing lung
260 transplantation or who are in intensive care [87-89]; a sensitivity of 100% and a specificity of 90.4%
261 was defined at cut-off of 1.5 [87].
262 (1-3)-β-D-glucan (BDG) is a constituent of the cell wall of many species and genera of fungi and is
263 released into body fluids in association with fungal infection. A limited role is given for the exclusive
264 testing of the BDG in diagnosing IA **(BII)** (Table 8), however, the combination with GM or PCR improves
265 specific detection [90].

The *Aspergillus* lateral flow LFD assay can be performed on serum and on BAL samples, but at the time of writing this assay is not commercially available [91] (Table 9).

Aspergillus PCR has been applied mostly to blood and BAL fluid. For both sample types, a combination with other biomarkers increases the likelihood of IA [92, 93]. The performance of serum PCR is not significantly different from that of whole blood [94-97]. Prospective screening of high-risk haematological patients by a combination of GM and PCR improves the diagnostic accuracy and is associated with an earlier diagnosis [98, 99] (Table 10 and 11).

On hyphal positive biopsy samples molecular detection of fungi is strongly recommended **(AII)**. If no hyphae are visible the diagnostic yield of molecular methods is lower (Table 12). Recommendations for storage of original samples and isolates are given in table 13. Antibody detection tests are not supported for the diagnosis of IA **(CII)** (Table 14).

Antifungal Susceptibility Testing

Resistance to antifungal agents is an increasing problem in *Aspergillus* diseases [100-102]. *Aspergillus* species can be intrinsically resistant to polyenes and azoles [103], or may acquire resistance following exposure to azole compounds [104]. Acquired resistance to azoles is mainly found in *Aspergillus fumigatus* and is reported globally [100, 101, 105-108]. Resistance may also develop through exposure to azole fungicides in the environment [109-112]. As resistant spores are present in ambient air, patients may present with azole-resistant *Aspergillus* disease without previous azole therapy [113, 114]. Individual *Aspergillus* colonies from a single specimen may harbour different resistance profiles [117], hence multiple colony testing (up to 5 colonies) is recommended to increase sensitivity for azole-resistance detection **(BIII**).

In clinical laboratories, species identification to complex level is recommended for all clinically significant isolates **(BIII)**. Some species are intrinsically resistant to either azoles or amphotericin B (AmB) (Tables 5, 15, 16 and 17).

Antifungal susceptibility testing of *Aspergillus* isolates should be performed in patients with invasive disease with the exception of azole naïve patients in regions with no resistance found in contemporary surveillance programmes and regularly for epidemiological purposes including ≥100 isolates. This is particularly important in patients who are unresponsive to antifungal treatment, or in patients who are clinically suspected having an azole-resistant pathogen **(AIII)** (Table 15). If MIC-testing is not available, routine agar screening can be used to detect azole resistance (Table 16) [118]. However, such isolate should be referred to a mycology reference laboratory for MIC testing. Clinical breakpoints for interpretation of azole and AmB MICs against *Aspergillus* are currently available for European Committee on Antimicrobial Susceptibility Testing (EUCAST) microdilution method but remain undetermined for Clinical & Laboratory Standards Institute (CLSI) methodology. Accordingly, EUCAST **(AII)** or CLSI broth microdilution methods **(BII)** can be used for determination of routine MICs for clinical guidance and for epidemiological resistance surveillance **(AII)**. Both itraconazole and voriconazole **(AII)** should be tested to ensure detection of the voriconazole-resistance mutation TR_{46}/Y121F/T289A [118]. Posaconazole resistance without itraconazole resistance has not been reported (Table 17). EUCAST **(BIII)** or CLSI broth microdilution methods **(CIII)** can be used to determine AmB MICs but although a correlation between MIC and clinical outcome exist for *A. terreus* and *A. flavus* it remains to be documented for *A. fumigatus* due to the scarcity of resistant isolates (Table 17).

Voriconazole and isavuconazole are recommended for the treatment of IA due to species showing high AmB MICs (Table 19). Liposomal AmB (L-AmB) or AmB lipid complex (ABLC) are recommended for species with intrinsic high azole MICs (Table 18 and 20). In aspergillosis due to *A. fumigatus* specifically, voriconazole or isavuconazole are recommended if the isolate is voriconazole susceptible (EUCAST MIC ≤1 mg/l) **(AI).** If resistant (voriconazole MIC >2 mg/l), L-AmB therapy is recommended **(AII_u).** It is unknown if patients infected with *A. fumigatus* with voriconazole MIC 2 mg/l (intermediate), respond less well to voriconazole monotherapy. These patients may have an increased probability of failing voriconazole monotherapy, and combination therapy with an echinocandin or L-AmB monotherapy

should be considered for invasive disease **(AIII)** (Table 20). In azole-resistant CPA, L-AmB or micafungin can be considered **(BII)** if surgical intervention is precluded [11]. In settings with environmental azole resistance, no change to the primary regimen for IA is recommended when resistance rates are <10% **(AIII).** If azole resistance rates are >10%, first line therapy with voriconazole plus echinocandin **(BIII)** or L-AmB **(BIII)** is recommended.

Therapeutic Drug Monitoring (TDM)

Patients with IA often have multiple conditions associated with their underlying disease and its treatment that affects the absorption, distribution, metabolism, and clearance of antifungal medications [119]. As a result, standardized dosing recommendations for antifungals used in the prevention or treatment of IA may not achieve effective or safe drug exposures in all patients. Moreover, a subset of patients with severe infections or difficult to treat sites (e.g. CNS) or infections caused by *Aspergillus* spp. with elevated MICs may require higher drug exposures. Therapeutic drug monitoring (TDM) is often the most direct laboratory approach for identifying patients at jeopardy for treatment failure or toxicity because of inadequate or excessive drug exposures, and can be used to fine-tune antifungal dosing to improve the probability of optimal outcomes (Table 21).

Itraconazole

For itraconazole, a serum trough of 0.5-4 mg/L (measured by HPLC) is recommended for prophylaxis **(AII [efficacy], BII [safety])** and a trough of 1-4 mg/L is recommended during the treatment of IA **(AII [efficacy], BII [safety])** [120-125]. Itraconazole has an active metabolite, OH-itraconazole that is present in similar (1:1) concentrations as the parent itraconazole compound when patients are at pharmacokinetic steady state. OH-itraconazole concentrations may be reported separately when samples are analysed by HPLC or LC/MS/MS, but will included in the overall report of "itraconazole" concentrations if samples are analysed by bioassay [126, 127]. Therefore, the target range for itraconazole is higher when reported by bioassay (i.e. 3-17 mg/L) but may vary by lab depending on

the reference standards used. Samples should be acquired within 5-7 days of starting therapy. Repeat TDM is recommended the following week to confirm the patient remains in the therapeutic range, and repeated thereafter as clinically indicated if there are changes in the patient's clinical condition, concomitant medications known to interact, or suspected toxicity (Table 22). Steady-state concentrations can often be predicted from earlier (non-steady) state samples through pharmacokinetic models or computerized dosage-assistance. In centres where these tools are available, sampling before day 5-7 may be preferable.

Voriconazole

A plasma trough concentration of 1-5.5 mg/L is considered adequate for most patients receiving voriconazole prophylaxis or treatment **(AII, safety and efficacy)** [128-133]. However, a trough of 2-6 mg/L **(AII, safety and efficacy)** is recommended in patients treated for severe infections (multifocal or disseminated disease, CNS infections, infection with pathogen with elevated MICs, e.g. an MIC of 2 ml/L) [130, 131]. TDM is strongly recommended in children due to the much higher rates of drug elimination and potential for underdosing, especially with the lower voriconazole doses recommended in the past **(AII)** [134, 135]. Plasma levels should be monitored between 2-5 days after initiation of therapy, and repeated the following week to confirm the patient remains in the therapeutic range. Repeated monitoring is indicated until steady state level in the therapeutic range is confirmed, if there are changes in the patient's clinical condition, concomitant medications, or suspected toxicity (Table 23).

Posaconazole

For patients receiving posaconazole suspension, a plasma trough of >0.7 mg/L is recommended during prophylaxis **(BII efficacy)** [136, 137]; and a trough of >1 mg/L is recommended if the patient is receiving treatment for suspected or documented IA **(AII efficacy)** [138]. Currently, no studies have defined an upper plasma target that is associated with toxicity, although pharmacokinetic studies supporting the

registration of the new posaconazole tablet and intravenous formulations with the EMA used a provisional cut-off of 3.75 mg/L [139-141]. Posaconazole plasma trough levels should be monitored on day 5 of therapy or soon thereafter, and repeated as clinically indicated.

For most patients prescribed posaconazole, we recommend using the newer tablet formulation (or intravenous formulation, if tablet formulation is contraindicated) rather than the suspension **(AII),** as tablets are more likely to consistently achieve target plasma levels and are less affected by GI-dependent drug interactions [139]. Currently, there is limited evidence to suggest that all patients receiving posaconazole tablets or IV formulation for prophylaxis require routine TDM**;** however, our opinion is that when treating suspected or documented *Aspergillus* infections, TDM could still be useful if the pathogen has elevated MICs, is unresponsive to treatment, or in the event of unexplained toxicity **(BIII).** Until further data are available, we recommend using TDM monitoring strategies and plasma trough targets as detailed above suggested for the suspension formulation (Table 24).

Isavuconazole

Although dose-response and plasma concentration-response relationships for isavuconazole have been reported in animal models, limited data are currently available to define a target therapeutic range or support the need for routine TDM for this agent [142]. Our opinion is that TDM could still be useful in the clinical assessment or monitoring of patients receiving isavuconazole therapy **(CIII)** if patients are unresponsive to treatment, have unexpected toxicity, pharmacokinetic drug-drug interactions, or if isavuconazole is being used to treat pathogens with elevated MICs or sanctuary sites such as the CNS. In the absence of well-defined therapeutic targets, documentation of a plasma trough in the range of 2-3 mg/L (mean concentration range from phase II/III clinical studies) after day 5 (including loading doses) suggests adequate drug exposure (Table 25).

Flucytosine

In rare circumstances, flucytosine may be used in combination with other antifungals for the treatment of triazole-resistant *Aspergillus* spp. In this scenario, weekly measurement of peak serum concentrations 2 hours following an oral dose **(AII)** are needed to confirm that peak concentrations are 50-100 mg/L in order to reduce the risk of toxicity. Trough concentrations required for efficacy are unknown but a level of 25-50 mg/mL is recommended based upon experience from cryptococcosis [143, 144].

Hospital Environment

Standards for the hospital environment in immunosuppressed adults and children requires special attention. Patients need to be segregated from construction or renovation **(AII$_h$)**, potted plants **(BII)**, and flowers in wards and in patients' rooms **(CIII)** [145-150]. Published data support the recommendation to accommodate patients in special hospital rooms with positive air pressure and HEPA filters **(BII)** or laminar airflow **(BII$_h$).** However, data were with historical controls, underpowered, or described by multivariate analysis describing high-risk situations for IA [151-154]. Protective masks for patients are proven not to be effective outside of the protected area **(CII)** [155]. Filters for water supply, especially in showers, are recommended **(BII)** [156-160]. No data are available to support regular environmental air sampling to prevent infections. However, indoor sampling is advisable to monitor filter efficacy **(BIII)** [161, 162].

Treatment Strategies

Two strategies are accepted for managing patients with haematological malignancy at risk for IA: 1) the patient receives primary prophylaxis or 2) the patient receives no prophylaxis but is monitored at least twice weekly using biomarkers. The decision between the two strategies depends on local epidemiology, access to rapid diagnostics and patient characteristics. Breakthrough fungal diseases may appear through either symptoms or a disease-identifying biomarker or imaging result. Figure 1 depicts a consensus algorithm for patient management.

Primary Prophylaxis

At least three studies describe a number of patients who succumbed with IA missed prior to death [163-165]. Although diagnostic procedures improved since then, they are not satisfactory. For this reason, patients known to be at high risk for IA may receive primary prophylaxis, especially patients with profound and prolonged neutropenia or with active graft-versus-host disease (GvHD) (Table 26).

Aspergillosis in Haematological Malignancy and Haematopoietic Stem Cell Transplantation

In patients treated for haematological diseases, prolonged severe neutropenia is the most important risk factor for the development of IA. T cell depleted grafts, glucocorticosteroids and other immune suppressive drugs have been identified as further risk factors for IA in the later course after HSCT, even in non-neutropenic patients [166]. In fact, up to two thirds of patients with IA diagnosed after allogeneic HSCT are not neutropenic [167], and the median time of diagnosis of IA after allogeneic HSCT is 82 days (range, 3 - 6542 days) [168].

Treatment

Providing a definite diagnosis of IA is a continuously challenging endeavour for clinicians. The EORTC/MSG definitions are only designed for clinical studies. For clinical decision-making, these definitions could have a deleterious outcome since confirmation of a proven or probable diagnosis would delay the start of therapy [169]. Any patient at risk considered by the responsible clinician as having IA should receive antifungal therapy **(AIII)** (Tables 27-28). Physicians should consider IV to oral switch in stable and PK-reliable patients. Treatment duration depends on clinical response and on immune reconstitution or recovery from GvHD. Good partial or complete remission requires no persistent clinical, including imaging (scarring allowed) or microbiological evidence of disease. The range of the duration of treatment (3 to >50 weeks) is huge and the evidence base to support any

particular recommendation is weak [170-173]. Close monitoring (e.g. non-enhanced CT or, if applicable, biomarkers) is suggested once antifungal treatment is discontinued.

Additional adjunctive therapy such as the administration of G-CSF or G-CSF-primed granulocyte infusions (data mainly from paediatric populations) received only a weak supportive recommendation (CIII). In refractory cases, G-CSF (or IFNγ) has immunomodulatory effects [174-179]. No controlled trials have been performed and only anecdotal data with small numbers of patients exist. Persistent neutropenia is related with treatment failure, recovery from neutropenia enhances the efficacy of antifungal agents. A recent Cochrane review investigating the efficacy of granulocyte transfusions indicated no mortality difference for any kind of infection in patients with neutropenia [180].

Fever-driven ("Empiric"), and Diagnosis-driven ("Pre-emptive") Therapy

As an alternative to prophylaxis, patients could receive the classical empirical administration of antifungal agents during fever refractory to broad-spectrum antibacterial agents. Empiric treatment is defined as a fever-driven treatment approach. Patients who would qualify for this approach are patients receiving induction or remission chemotherapy for acute leukaemia or MDS or conditioning chemotherapy for haematopoietic stem cell transplantation. Empiric antifungal treatment is expected to reduce morbidity [181-186] and mortality [187, 188] (Table 29). The duration of empiric antifungal treatment is set by the following rules applied in randomized clinical trials: If the patient is afebrile and has no active infection or infiltrates, then antifungal therapy can be discontinued after recovery of leukocyte counts [188-190]. Today, antifungal stewardship may warrant clinical trials on empiric treatment duration, but no such trial has been conducted so far.

Pre-emptive treatment is a diagnosis driven strategy. In most cases, it is defined by positive GM testing. However, chest CT with pulmonary infiltrates could apply as well. The use of BDG and PCR testing as alternative biomarkers for galactomannan have considerable merit [191, 192], though BDG is not specific for *Aspergillus* disease. In haematological patients, false positive BDG often results from contaminated infusions [193-196]. Very few authors wait for *Aspergillus*-associated suggestive

radiological signs including nodule, halo sign, wedge-shaped area of consolidation, or – late in the course of invasive aspergillosis – the air crescent sign, before starting antifungal treatment. Treatment choices are as recommended in targeted treatment.

Adult Patients without Haematological Malignancy

Epidemiology

Approximately 43-80% of the cases of IA appear in patients without a haematological malignancy [52, 197-200], although these patients are rarely included in the seminal studies of antifungals [170, 171, 173]. The proportion of these patients is even increased when exposed to spore concentrations of >25 cfu/m^3 in hospital air [201-204]. The non-haematological populations at risk for IA include solid organ transplant recipients (SOT), patients treated with prolonged high dose glucocorticosteroids, or with other immunosuppressants, patients with advanced AIDS or neoplasia, COPD, liver failure, liver cirrhosis, influenza as well as critically ill patients requiring ICU admission [52, 197-199, 205-208]. These patients frequently do not fulfil the EORTC/MSG criteria for invasive aspergillosis [169]. Confirmation of diagnosis may be delayed resulting in high mortality rates. At the same time drug-drug interactions and toxicity can occur more frequently compared to haematological patients [52]. Physicians need to be aware of the specific risk factors, clinical manifestations and management challenges in order to improve outcome. In SOT recipients the average incidence of IA ranges from 0.1 to 11.6% [209, 210], with the highest risk in small bowel (11.6%) and lung (8.6%) transplant recipients, followed by patients receiving liver (4.7%), heart (4.0%), pancreas (3.4%), and kidney (1.3%) grafts [209-211]. Half the cases will occur in the first three months after transplantation, in patients with post-surgical risk factors. Late aspergillosis is more common in elderly recipients, and patients with pronounced immunosuppression due to rejection or post-transplant neoplasia or chronically impaired graft function [210, 212]. With the exception of lung transplantation, in which universal prophylaxis is still common, antifungal prophylaxis will target SOT recipients with additional risk factors [211]. Risk factors for early IA in all SOT recipients – Including heart transplants – comprise renal failure requiring

497 replacement therapy, re-intervention, CMV disease, and high environmental exposure to mould
498 spores [211, 213-215]. In liver transplantation, high model for end-stage liver disease (MELD) score,
499 transplantation in fulminant hepatic failure, high intraoperative transfusion needs or re-
500 transplantation are considered indications for post-surgical prophylaxis [216-224]. In lung transplant
501 recipients, risk factors include previous respiratory tract colonization with *Aspergillus,* single lung
502 transplant, CMV disease and acquired hypogammaglobulinaemia [225-227]. In kidney transplantation
503 risk factors include COPD, delayed graft function, bloodstream infection, and acute graft rejection
504 [228] and an >1.25 mg/kg/day average dose of prednisone [229]. Finally, some polymorphisms in
505 defence genes have also been suggested to increase risk in transplant recipients [230, 231].
506 The incidence of IA in HIV patients has decreased since the advent of new antiretroviral therapy (2.2
507 cases per 10,000/year), but mortality remains high (38%) [232]. IA typically appears in patients with
508 low CD4 counts and associated conditions such as neutropenia, advanced cirrhosis, liver
509 transplantation or glucocorticosteroid therapy [233-241]. As in other non-haematological populations,
510 EORTC/MSG criteria only detect half of the IA cases diagnosed among HIV-infected patients [232] and
511 in a recent series of autopsies of AIDS patients, only 12% of the patients with IA had been diagnosed
512 ante mortem [242] (Table 30).
513 IA may affect 0.3% of patients with liver cirrhosis [243]. Both acute liver failure and advanced cirrhosis,
514 mainly alcoholic hepatitis treated with glucocorticosteroids, have been recognized as risk factors for
515 IA [205, 244-246]. A low level of clinical suspicion explains that 53% of the cases of IA in cirrhotic
516 patients are only recognized post-mortem [247] and that liver disease is independently associated with
517 IA-related mortality [199, 248].
518 IA has also been described in apparently immunocompetent patients in a critical condition as a
519 complication of ARDS, COPD, influenza, pneumonia, burns, severe bacterial infection, surgery, and
520 malnutrition. Incidence is 4-6/1,000 ICU admissions and the mortality is higher than 70% in most series
521 [245, 249-252]. Glucocorticosteroid treatment was the major host factor [253, 254] and as in cirrhotic
522 or HIV positive patients delayed diagnosis is common [255, 256]. COPD patients requiring

glucocorticosteroids represent a group with especially high mortality [249, 257 , 258]. Risk factors include admission to ICU, chronic heart failure, and antibiotic treatment and, above all, the cumulative dose of glucocorticosteroids [257].

Pulmonary and CNS aspergillosis predominates in these populations, but disseminated disease, fulminant and atypical forms may occur [203, 214, 225, 251, 259-267]. The sensitivity of most diagnostic methods is lower in non-haematological patients. Isolation of *Aspergillus* from respiratory cultures has a much lower positive predictive value so over-diagnosis has to be prevented [197, 268-272]. Regarding imaging findings, angioinvasive presentation included in the EORTC/MSG criteria is uncommon in this setting [273]. Airway invasive radiological presentation was present in 37% of heart transplant recipients and was associated with delayed diagnosis and poorer prognosis [214, 274]. In COPD and HIV-positive patients, the most common radiological presentation was an alveolar infiltrate [273, 275, 276]. Experience with biomarkers and PCR is still scarce in these populations, but the combination of at least two different methods appears to be the best diagnostic approach [277-285] (Table 31).

Treatment

Despite no comparative studies of antifungal therapy in non-haematological patients voriconazole remains the first option, since it has been related to reduced mortality [216, 286-288] (Table 32). Combination therapy is uncommon, although retrospective data was encouraging in SOT recipients [289]. The risks of drug-drug interactions and toxicity are very important in these populations and TDM is advisable [290-295]. In patients with liver insufficiency, L-AMB is usually the first therapeutic option. Antifungal resistance is not a common problem despite prophylaxis [296, 297], although some cases have been reported [298-300]. Finally, immune reconstitution syndrome may occur after therapy initiation [301].

Most lung recipients receive antifungal prophylaxis. Targeted prophylaxis is preferred in the remaining SOT with risk factors [211, 213, 302-305]. However, significant variation in practice has been noted

549 [221, 304, 306, 307]. In order to avoid drug-drug interactions and toxicity, echinocandins or inhaled
550 amphotericin are preferentially used [308-311], although voriconazole has also demonstrated its
551 efficacy and safety in this setting [217, 220, 312-314]. Duration of prophylaxis is adjusted to the
552 presence of risk factors and, with the exception of lung recipients, is usually limited to 3-4 weeks [215]
553 (Table 33).
554
555 **Special Considerations in Children**
556 Presenting symptoms, distributions and patterns of diseases and vulnerability to IA are similar
557 between children and adults. However, differences exist in epidemiology and underlying conditions,
558 usefulness of newer diagnostic tools, pharmacology of antifungal agents and evidence from
559 interventional phase III studies. Recommendations for paediatric patients are based on efficacy in
560 phase II and III trials in adults, the availability of paediatric pharmacokinetic data, safety data and
561 supportive efficacy data. In addition, regulatory approval is considered as well. Therapeutic drug
562 monitoring is always recommended when mould-active azoles are used as prophylaxis or treatment.
563 Primary antifungal prophylaxis may be indicated in paediatric patients at 'high risk' for developing
564 invasive fungal diseases, and specifically IA. An incidence rate of IFDs of ≥10% is usually considered as
565 high risk. High-risk populations include children with de novo or recurrent leukaemia (e.g. AML, ALL
566 depending on treatment protocol), bone marrow failure syndromes with profound and persistent
567 neutropenia (e.g. MDS, VSAA), allogeneic HSCT recipients, patients with chronic granulomatous
568 disease and those undergoing lung transplantation. For patients with haematological disorders, the
569 mould-active oral azoles are the first choice to prevent IA in children, although neither itraconazole
570 nor posaconazole are licensed for use in patients <18 years of age. Due to the lack of paediatric data,
571 recommendations for lung and high-risk liver transplant patients correspond to those given for adults
572 [213, 315]. Secondary prophylaxis to prevent recurrence of IA when risk factors are persisting is
573 recommended with an antifungal targeted at the previous *Aspergillus* species, which caused the first
574 episode (see below and Table 34).

575 Diagnostic procedures used in children are not different from those used in adults but their
576 performance may differ. Suggestive abnormalities (e.g. halo sign, air crescent sign) on CT-chest as
577 described in adults are less common in children in which non-specific masses or infiltrates predominate
578 [316-318]. The GM test on blood and BAL samples has a similar sensitivity and specificity profile
579 compared to adults [319-327]. The BDG test is not specific for *Aspergillus* and is not validated in
580 children. Higher baseline levels are reported in healthy children and therefore the cut-off is yet
581 unknown [328-332].
582 General management principles of IA are consistent with those in adults and include prompt initiation
583 of antifungal therapy, control of predisposing conditions (e.g. reduction or discontinuation of
584 glucocorticosteroids in immunosuppressed, administration of colony-stimulating factors in
585 neutropenic patients), and surgical interventions on a case by case basis using a multidisciplinary
586 approach. Voriconazole is recommended as the first line agent to treat IA in all children except
587 neonates **(AIIt)**. L-AmB is first choice for neonates **(AIII)** and may replace voriconazole as first line
588 treatment in areas or institutions with a high prevalence of azole-resistant *A. fumigatus*. Upon
589 diagnosis of invasive pulmonary aspergillosis, thorough evaluation for further sites of infection is
590 required and should include the CNS. The optimal duration of therapy is determined by the resolution
591 of all signs and symptoms and reversal of the underlying deficit in host defences. For salvage therapy
592 and breakthrough infections, a switch to a different class of antifungals is recommended [123, 132,
593 138, 170, 171, 177, 333-341] (Table 35).
594 If a fever-driven (empiric) strategy is used in at risk paediatric haematological patients, caspofungin or
595 L-AmB are recommended until resolution of fever and neutropenia [342-344]. Treatment
596 recommendations for a diagnosis-driven (pre-emptive) strategy correspond to those made for
597 targeted treatment [185, 186, 345, 346].
598
599 **Secondary Prophylaxis**

Secondary prophylaxis is a treatment strategy to prevent recurrence of IA during a subsequent risk period of immunosuppression. Patients with a history of IA previously successfully treated with antifungals entering a subsequent risk period of immunosuppression, e.g. allogeneic HCT (early phase), chemotherapy resulting in severe neutropenia (i.e. <500/µL and at least for 7 days), acute GvHD >I° or extensive chronic GvHD, or T-cell suppressing therapy, including steroids, are at risk. Agents for secondary prophylaxis are listed in table 36.

Treatment of Refractory Disease

Refractory IA is defined as progression of disease and should be differentiated from stable disease [349]. Patients with radiological evidence of progression and persisting elevated GM have a very high probability of treatment failure resulting in death. Assessment of response should use composite outcome parameters including clinical, radiological, and mycological criteria. Radiological progression following or closely preceding neutrophil recovery should be carefully evaluated and is not necessarily indicative of failure. Keeping this in mind, assessing response 2 weeks after treatment initiation generally allows predicting the response, especially recognizing oncoming failure [350]. In case of GM negative IA, early assessment of response may be difficult and could require a longer time of therapy. If failure ascertained, look for poor vascular supply (i.e. sinusitis requiring surgical treatment), microbiological confirmation is recommended since identification of the fungus at the species level is pivotal. If a viable organism is recovered, susceptibility testing is recommended, especially regarding azole resistance. On the other hand, azole concentration should be monitored as well (see chapters on resistance and therapeutic drug monitoring within this guideline) [38, 349, 351-359]. The choices of antifungal agents in refractory disease are listed in table 37.

Chronic Pulmonary Aspergillosis (CPA)

CPA is an indolent destructive disease of the lungs usually complicating other pulmonary conditions occurring in non- or mildly immunocompromised patients [360, 361]. Its manifestations include

chronic cavitary pulmonary aspergillosis (CCPA), which if left untreated may progress to chronic fibrosing pulmonary aspergillosis (CFPA), *Aspergillus* nodule and single aspergilloma [11, 362]. Subacute invasive pulmonary aspergillosis (previously chronic necrotizing pulmonary aspergillosis) is also a cavitating destructive lung disease usually found in moderately immunocompromised patients which progresses more rapidly, typically over 1 to 3 months. The diagnosis of CPA requires a combination of characteristics: one or more cavities with or without a fungal ball present or nodules on thoracic imaging, either direct evidence of *Aspergillus* infection (culture or microscopy from biopsy) or an IgG antibody response to *Aspergillus* spp. and exclusion of alternative diagnoses (especially mycobacterial infection), all present for at least 3 months [11, 363]. Over 90% of patients have circulating *Aspergillus* antibody (precipitins) **(AII)** [364]. A positive culture of *A. fumigatus* respiratory tract secretion (BAL, bronchoscopy aspiration) is not diagnostic because many different pathologies are attributable to the fungus, and it may be an airway colonizing fungus or a plate contaminant in the laboratory.

If a fungal ball is seen, then only a positive test of *Aspergillus* IgG or precipitins confirms pathogenicity. Patients may have CPA and other infections concurrently (see below).

The distinctive hallmark of CCPA is new and/or expanding cavities with thick or thin walls in those with chronic lung disease. An intracavitary fungal ball may be present, often with pleural thickening and extensive parenchymal destruction and/or fibrosis. Patients may have CPA and other infections concurrently, especially bacterial including *Pseudomonas aeruginosa* infection or tuberculosis and non-tuberculous mycobacterial infection. *Aspergillus* nodules, which may be single or multiple, may mimic malignancy as well as nodules seen in rheumatoid arthritis, coccidioidomycosis, tuberculosis, non-tuberculous mycobacterial infection and – rarely – actinomycosis or rheumatoid arthritis. Typically, *Aspergillus* nodules appear rounded, some with low attenuation or cavitation within. Some are spiculated, a common feature of carcinoma [362].

If technically feasible single aspergilloma should be surgically removed, preferably via video-assisted thoracic surgery technique with due consideration to risks as recommended [365]. Long term oral

antifungal therapy is strongly recommended in patients with CCPA, partly to reduce general and respiratory symptoms [366, 367], but also to minimise haemoptysis and prevent lung destruction and fibrosis **(AII)** itraconazole or voriconazole are effective for CCPA **(AIII)** [11]. Oral posaconazole is a potential alternative treatment **(BII)** [11]. Six months of therapy is the recommended minimum **(AI)** [11]. Relapse is common after discontinuation. Intravenous therapy for CPA is useful in patients who fail or are intolerant of triazoles or have triazole resistant *A. fumigatus*. Prednisolone may be considered for underlying symptom control only if patients are adequately treated with antifungals. Mild and moderate haemoptysis usually responds to tranexamic acid; severe haemoptysis should be arrested with bronchial artery embolization (Table 38).

Conclusions

This executive summary is a comprehensive guideline covering many aspects of *Aspergillus* diseases. It provides guidance for clinicians on prevention of disease, diagnostic procedures, resistance issues and treatment of IA as well as chronic pulmonary aspergillosis. The guideline group intends to provide additional publications supporting the rationale of recommendations given.

Finally, the guideline group provides comprehensive tables explaining various options for specific situations.

669 **Table 1. Strength of recommendation and quality of evidence**

Strength of Recommendation (SoR)	**Definition**
Grade A	Societies strongly support a recommendation for use
Grade B	Societies moderately support a recommendation for use
Grade C	Societies marginally support a recommendation for use
Grade D	Societies support a recommendation against use
Quality of Evidence (QoE)	**Definition**
Level I	Evidence from at least 1 properly* designed randomized, controlled trial (orientated on the primary endpoint of the trial)
Level II	Evidence from at least 1 well-designed clinical trial (incl. secondary endpoints), without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees
Added Index	**Source of Level II Evidence**
r	Meta-analysis or systematic review of RCT
t	Transferred evidence i.e. results from different patients‘ cohorts, or similar immune-status situation
h	Comparator group: historical control
u	Uncontrolled trials

a	For published abstract presented at an international symposium or meeting
* poor quality of planning, inconsistency of results, indirectness of evidence etc. would lower the SoR	

670

671 **Table 2. Recommendations for imaging and bronchoalveolar lavage**

Population	Intention	Intervention*	SoR	QoE	Comment	Ref.
Neutropenia, fever or clinical symptom of pneumonia, empiric antibiotics, failing to achieve defervescence, e.g. FUO	To detect pulmonary infiltrates	Chest CT and thin section multi-detector CT (MDCT)	A	II	Within 12-24h after the beginning of fever, dose optimization recommended	[21, 31, 35, 368]
Haemoptysis	To identify vessel occlusion	Chest angio-CT / pulmonary CT angiography	B	II		[24-26]
Haemoptysis	To identify vessel erosion	Chest angio-CT / pulmonary CT angiography	A	II		[24-26, 369, 370]

Any	To identify possible underlying fungal or other infectious disease	BAL	A	II		[21, 49-54]
Any	To obtain appropriate specimens for microscopy, culture and PCR	CT-guided BAL	A	III		[55, 56]

*, Diagnostic tests are interventions; SoR, Strength of recommendation; QoE, Quality of evidence; FUO, fever of unknown origin; CT, computed tomography; BAL, bronchoalveolar lavage; PCR, polymerase chain reaction

675 **Table 3. Microscopic examinations**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	To identify fungal elements in histological sections and stains	Histological examination Gomori's methenamine silver stain Periodic acid-Schiff	A	III	Histopathology is an essential investigation Inability to definitively distinguish other filamentous fungi GMS: removes cellular background; more sensitive to hyphal elements PAS: advantage of counter stain to check cellular detail	[80, 371-373]
Any	To identify fungal elements in histological sections and stains	Fluorescent dyes: Calcofluor white™, Uvitex 2B, Blancophor™	A	II	Not specific to *Aspergillus* but high sensitivity and the micromorphology may provide info on the fungal class (e.g. *Aspergillus*: typically dichotomous and septate, Mucorales: pauci-septate and 90° angle branching, yeast: budding) Rapid turnaround time Broad applicability May be applied to frozen sections, paraffin-embedded tissue	[374-378]

Any	To identify fungal elements in histological sections and stains	Immunohistochemistry Monoclonal antibody WF-AF-1 or EB-A1 In situ hybridization	B	II	Have the potential to provide genus and species specific data Commercially available monoclonal antibodies WF-AF-1 is specific for *A. fumigatus*, *A. flavus*, and *A. niger* Time consuming and not broadly available	[374-378]
Any	To identify fungal elements in fresh clinical specimens (e.g. BAL)	Application of fluorescent dyes Calcofluor white™ or Uvitex 2B or Blancophor™	A	II	Essential investigation Not specific for *Aspergillus* species High sensitivity Rapid turn-around time Broad applicability No species identification but the micromorphology may provide info on the fungal class (e.g. *Aspergillus*: typically dichotomous and septate, Mucorales: pauci-septate and 90° angle branching, yeast: budding)	[80, 373, 379]

676 SoR, Strength of recommendation; QoE, Quality of evidence; BAL, bronchoalveolar lavage; HE, haematoxylin-eosin; GMS, Gomori's methenamine silver
677 stain; PAS, Periodic acid-Schiff; CNS, central nervous system
678

Table 4. Sample selection and pre-analytical respiratory sample treatment

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	To achieve a homogenous sample of viscous samples such as sputum	Liquefaction using a mucolytic agent, e.g. Pancreatin®, Sputolysin®, or using sonication and 1,4-dithiothreitol	A	III	Essential investigation High volume sputum culture (entire sample) shown to significantly increase recovery	[81, 380]
Any	To achieve optimal recovery of *Aspergillus* from BAL by centrifugation and investigation of the sediment	Centrifugation of BALs or bronchial aspirates	A	III	Essential investigation Isolation of *Aspergillus* dependent on volume cultured	[81]

SoR, Strength of recommendation; QoE, Quality of evidence; BAL, bronchoalveolar lavage; PCR, polymerase chain reaction

682 **Table 5. Culture and *Aspergillus* species identification**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	Primary isolation from deep sites samples (e.g. biopsies, blood, CSF)	Culture on SDA, BHI agar, PDA at 30ºC and 37ºC for 72 h	A	III	Blood inhibits conidiation; BHI can help to recover some isolates; Isolation of several colonies or isolation of the same fungus from a repeat specimen enhance significance	[81, 381, 382]
	Primary isolation from non-sterile samples, e.g. sputum, respiratory aspirates	Culture on SDA, BHI agar, PDA with gentamicin plus chloramphenicol at 30ºC and 37ºC for 72 h	A	III	High volume sputum culture (entire sample) shown to significantly increase recovery; Quantitative cultures are not discriminative for infection or colonization	
	Identification of species complex	Macroscopic and microscopic examination from primary cultures	A	II	Colony colour, conidium size, shape and septation. Colour of conidia and conidiophore and conidiogenesis (tease or tape mounts are preferred); Expertise needed for interpretation	
	Identification of species complex (and species	Culture on identification media at 25-30ºC, 37ºC	A	II		

	identification of *A. fumigatus* specifically)	and 50ºC (2% MEA and Czapek-Dox Agar) and microscopic examination			Thermotolerance test (growth at 50 °C for species confirmation of *A. fumigatus*)	
	Identification at species level	MALDI-TOF MS identification	B	II	In house databases are often used to improve identification rates	[383-386]
	Identification at species level	Sequencing of ITS, beta-tubulin and calmodulin	A	III	Not necessary in organisms with typical growth, but in cases of atypical growth	[387, 388]
	To study outbreaks	Microsatellite and CSP analysis	C	II	To study outbreaks (which in general may comprise more than one genotype)	[389-391]
			B	II	To study colonisation patterns	[392]

SoR, Strength of recommendation; QoE, Quality of evidence; CSF, cerebrospinal fluid; SDA, Sabouraud dextrose agar; BHI, brain heart infusion; PDA, potato dextrose agar; MEA, malt extract agar; MALDI-TOF MS, matrix-assisted laser desorption ionization time-of-flight mass spectometry identification; ITS, internal transcribed spacer; CSP, Cell surface protein

683

684 **Table 6. Galactomannan testing in blood samples**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Patients with prolonged neutropenia or allogeneic stem cell transplantation recipients **not on mould-active prophylaxis**	Prospective screening for IA	GM in blood*	A	I	Highest test accuracy requiring 2 consecutive samples with an ODI ≥ 0.5 or retesting the same sample Prospective monitoring should be combined with HRCT and clinical evaluation	[82, 94, 393-397]
		Draw samples every 3-4 days	C	III		
Patients with prolonged neutropenic or allogeneic stem cell transplantation recipients **on mould active prophylaxis**	Prospective screening for IA	GM in blood*	D	II	Low prevalence of IA in this setting with consequently low PPV of blood GM test Prophylaxis may have a negative impact on sensitivity of the test or the low yield may be due to decreased incidence of IA	[398, 399]
Patients with a haematological malignancy • Neutropenic patients • Non-neutropenic patients	To diagnose IA	GM in blood*	 A B	 II II	Significantly lower sensitivity in non-neutropenic patients	[319, 394, 400, 401]

ICU patients	To diagnose IA	GM in blood*	C	II	Better performance in neutropenic than in non-neutropenic patients	[89, 402]
Solid organ recipients	To diagnose IA	GM in blood*	C	II	Low sensitivity, good specificity Most data for lung SOT	[319, 403, 404]
Any other patient	To diagnose IA	GM in blood*	C	II	Piperacillin/tazobactam may no longer be responsible for false positive results according to recent studies Cross reactivity in case of histoplasmosis, fusariosis, talaromycosis (formerly: penicilliosis)False positive results reported due to ingestion of ice-pops, transfusions, antibiotics, Plasmalyt® infusion	[401, 405-412]
Cancer patients	To monitor treatment	GM in blood*	A	II		[85, 359, 413]

685 SoR, Strength of recommendation; QoE, Quality of evidence; *, serum or plasma; GM, galactomannan; IA, invasive aspergillosis; ICU, intensive care unit;

686 ODI, optical density index; PPV, positive predictive value; SOT, solid organ transplantation

687

688 **Table 7. Galactomannan testing in samples other than blood**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	To diagnose pulmonary IA	To apply GM test on BAL fluid	A	II	GM in BAL is a good tool to diagnose, optimal cut-off to positivity 0.5 to 1.0	[86, 414-418]
Any	To diagnose cerebral IA	To apply GM test on cerebrospinal fluid	B	II	No validated cut-off	[419, 420]
Any	To detect GM in tissue	To apply GM test on lung biopsies	B	II	Using a cut-off 0.5 resulted in a sensitivity of 90 % and a specificity of 95%; specimens need to be sliced, precondition for doing so is that sufficient material is available; dilution in isotonic saline	[373, 421]

689 SoR, Strength of recommendation; QoE, Quality of evidence; BAL, bronchoalveolar lavage; GM, galactomannan; IA, invasive aspergillosis

690

691 **Table 8. *ß*-D-glucan assays**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Mixed population: adult ICU, haematological disorders, SOT	To diagnose IFD	Diagnostic assay	C	II	5 different assays Overall sensitivity of 77% and specificity of 85% Specificity limits its value in this setting	[90, 422]
		Screening assays	C	II	Two or more consecutive samples: sensitivity: 65%; specificity: 93% Studies included once to thrice weekly. Varies with assay and cut-off: Wako assay sensitivity: 40-97%, specificity: 51-99%	[90, 422]
Adult haematological malignancy and HSCT	To diagnose IFD	Diagnostic assay	C	II	Overall sensitivity: 50-70%, specificity: 91-99%	[193-195, 423-428]
ICU – mixed adult immunocompromised patients (haematology, SOT,	To diagnose IA	Diagnostic assay	C	II	Overall sensitivity: 78 -85%, specificity: 36-75%, NPV: 85-92% Specificity increased at higher cut-off values	[429, 430]

cancer, immunosuppressive therapy, liver failure, HIV)						
ICU – mixed adult population: SOT, liver failure, immunosuppressed		Screening assays	C	III	Sensitivity: 91%, specificity: 58%, PPV: 25%, NPV: 98%. Positive mean of 5.6 days before positive mould culture High false positive rate in early ICU admission	[431]
Adult haematological malignancy and HSCT	To diagnose IA	Diagnostic assay	C	II	Overall sensitivity: 57-76%, specificity: 95-97%	[422, 423, 429]
		Screening assays	C	II	Overall sensitivity: 46%, specificity: 97% Confirmation with GM increases specificity Data suggests BDG is unsuitable for ruling out diagnosis of IA	

692 SoR, Strength of recommendation; QoE, Quality of evidence; HSCT, haematopoietic stem cell transplantation; ICU, intensive care unit; SOT, solid organ
693 transplantation; IFD, invasive fungal disease; PPV, positive predictive value; NPV, negative predictive value; GM, galactomannan; BDG, ß-D-glucan test; IA,
694 invasive aspergillosis

Table 9. Lateral flow device antigen test for IA

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Haematological malignancy and solid organ transplant	To diagnose IA	LFD applied on BAL samples	B	II	Retrospective study. Sensitivity and specificity of BAL LFD tests for probable IPA were 100% and 81% (PPV 71%, NPV 100%), 5 pts with possible IPA had positive LFD, no proven IA	[432]
Haematopoietic stem cell transplantation	To diagnose IA	LFD applied on serum samples	B	II	Prospective screening in 101 patients undergoing allogeneic HSCT	[433]
Immunocompromised patients	To diagnose IA	LFD applied on BAL samples	B	II	Retrospective study. Sensitivities for LFD, GM, BDG and PCR were between 70 and 88%. Combined GM (cut off >1.0 OD) with LFD increased the sensitivity to 94%, while combined GM (cut off >1.0 OD) with PCR resulted in 100% sensitivity (specificity for probable/proven IPA 95-98%).	[434]

SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; BDG, *ß*-D-glucan test; BAL, bronchoalveolar lavage; GM, galactomannan; HSCT, haematopoietic stem cell transplantation; IFD, invasive fungal diseases; LFD, lateral device flow; NPV, negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value

700 **Table 10. PCR on bronchoalveolar lavage or cerebrospinal fluid**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Patients undergoing allogeneic stem cell transplantation recipients not on mould-active prophylaxis	To diagnose IA	BAL PCR	B	II		[435]
Patients with pulmonary infiltrates and haematological malignancies and prolonged neutropenia	To diagnose IA	BAL PCR	B	II	Methodically different in-house assays, better performance in patients without antifungal treatment, PCR and galactomannan: increases specificity	[359, 415, 434, 436-456]

ICU patients, mixed populations	To diagnose IA	BAL PCR	B	II	Commercially available Aspergillus PCR assays with good performance data.	[81][414][454][457][458][459]
Patients with haematological malignancies	To diagnose CNS aspergillosis or meningitis	CSF PCR	B	II	113 CSF samples from 55 immunocompromised patients sensitivity 100%, specificity 93% (retrospective)	[419, 460-463]

701 SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis ; BAL, bronchoalveolar lavage; PCR, polymerase chain reaction; ICU,

702 intensive care unit; CNS, central nervous system; CSF, cerebrospinal fluid.

703

704 **Table 11. PCR on whole blood, serum or plasma**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Patients with haematological malignancies	To diagnose IA	PCR on blood samples	B	II	Meta-analysis: 16 studies PCR single positive test: Sensitivity: 88%, specificity: 75%; PCR 2 consecutive positive tests: Sensitivity: 75%, specificity: 87%	[464]
	To diagnose IA	PCR on serum samples			97% of protocols detected threshold of 10 genomes/ml serum volume >0.5 ml, elution volume <100 µl, sensitivity: 86%; specificity: 94%	[465]
	To diagnose IA	PCR on whole blood samples			First blood PCR assay to be compatible with EAPCRI recommendations, fever driven: Sensitivity: 92%, specificity: 95%, negative PCR result to be used to rule out IA	[466]
Haematopoietic stem cell transplantation	To diagnose IA	Prospective screening PCR on whole blood samples	B	II	Combination of serum and whole blood superior	[94-97]

	To diagnose IA	Prospective screening PCR on blood samples	B	II	Addition of GM and PCR monitoring provides greater accuracy, PPV 50-80%, NPV 80-90%	[98]
	To diagnose IA	PCR and GM in BAL	A	II		[396]

SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; PCR, polymerase chain reaction; EAPCRI, European *Aspergillus* PCR Initiative; GM, galactomannan, PPV, positive predictive value; NPV, negative predictive value; BAL, bronchoalveolar lavage

708 **Table 12. Molecular diagnostics on biopsies**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Biopsy with visible hyphae	To detect and specify a fungus	Broad range PCR	A	II	High sensitivity (> 90 %) and high specificity (99 %); various molecular based techniques available	[373, 467]
Biopsy with no visible hyphae	To detect and specify a fungus	Broad range PCR	C	II	Sensitivity (57 %) and specificity (96 %); ability to distinguish other fungi; performance only in addition to other tests	[373, 467]
Biopsy with visible hyphae	To detect and specify a fungus	Broad range PCR on wax embedded specimens	A	II	TaKaRa DEXPAT kit and QIAamp DNA mini kit detected less than 10 conidia/sample	[468, 469]
Any	To detect and specify a fungus	Fresh tissue samples	B	II	*Aspergillus* PCR performance analysis yielded sensitivity/specificity rates of 86% / 100% (79 patients, retrospective study)	[58]

709 SoR, Strength of recommendation; QoE, Quality of evidence; PCR, polymerase chain reaction

710 **Table 13. Storage of original samples and isolates**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	To prevent loss of viability of *Aspergillus* in clinical samples, and to reflect the original fungal content	Clinical samples for culture - short-term storage: 4°C to prevent loss of viability and to reflect the original fungal content	A	III		[98, 381]
	To prevent degradation of biomarkers, e.g. GM in serum or BALs or bronchial washes	Complete assay soon after delivery to laboratory. Avoid short or long-term storage of serum at 4°C	A	I	GM in serum degrades with short-term and long-term storage at 4°C; BAL fluid GM ODI remain stable; testing of pos./neg. serum and BAL fluid pools showed no decline in GM index over 11 months at -20°C	[80, 371-373, 395]
	Short-term maintenance of *Aspergillus* isolates	Repeated sub-culture	A	I	Viability maintained for several years by frequent sub-culture; Transfer once a month; Maintain at average ambient room temperature	[98, 381]

	Long-term preservation of *Aspergillus* isolates	Water storage/storage under mineral oil/silica gel storage/freeze-drying freezing (-80°C/ceramic beads/liquid nitrogen)	A	I	Long-term storage means storage periods of 5 years or longer; No further transfers required during this period	

711 SoR, Strength of recommendation; QoE, Quality of evidence; GM, galactomannan; BAL, bronchoalveolar lavage; ODI, optical density index

712

713 **Table 14. Antibody based diagnosis of invasive aspergillosis[11]**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	To diagnose IA	*Aspergillus*-specific antibodies by EIA: Serion (Germany), Omega (France), Bio-Rad (France), Dynamiker (China)	C	II	Antibodies take a mean of 11 days to develop after onset of illness; detectable in 29% to 100% of patients during course of acute IA	[470-477]
		Precipitating antibodies by agar gel double diffusion (Microgen Ltd. UK) or counter-immuno-electrophoresis	C	III	Consider false-negative results due to hypogammaglobulinaemia	[478]
		Agglutinating antibodies by indirect haemagglutination (EliTech/Fumouze, France)	C	II		[478]
		Specific immunoglobulins to *Aspergillus* by ImmunoCap®	C	III		No reference found

714 SoR, Strength of recommendation; QoE, Quality of evidence; EIA, enzyme immunoassay; IA, invasive aspergillosis

715 **Table 15. Indications for testing for azole resistance in clinical *Aspergillus* isolates**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
All clinically relevant *Aspergillus* isolates (in patient groups or regions with known azole resistance)	Identify azole resistance	Reference MIC testing	A	II	In situations where rapid testing is available	[105, 111, 114, 116, 300, 479-489]
Clinically relevant *Aspergillus* isolates in patient groups with high prevalence of azole resistance or patients unresponsive to treatment	Identify isolates with intrinsic resistance	Species identification to complex level	A	III	Some species are intrinsically resistant – e.g. *A. calidoustus* (azole resistant) *and A. terreus* (AmB resistant)	[103, 490]
Clinically relevant *A. fumigatus* isolates	Identify azole resistant *A. fumigatus*	Routine azole agar screening	B	III	Identifies resistant colonies that require MIC-testing	[118, 491]
All isolates –resistance surveillance	Determine the local epidemiology of azole resistance	Periodical reference MIC testing of *A. fumigatus* complex	A	II	Test at least 100 isolates	[105, 111, 114, 300,

						482-485, 487-489]
Azole-resistant isolates	Determine nature and trends in Cyp51A mutation distribution	Cyp51A-gene mutation analysis	A	II	Test resistant isolates from surveillance survey	[107]

716 SoR, Strength of recommendation; QoE, Quality of evidence; AmB, Amphotericin B; MIC, minimum inhibitory concentration

717 **Table 16. Azole susceptibility testing: Timing, methods, and number colonies**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	Confirm or reject azole resistance in clinical *A. fumigatus* isolates when antifungal treatment is considered	Azole agar screening test followed by reference MIC test where needed	A	III	MIC testing as soon as the strain is isolated and without waiting for species ID	[103, 114]
	Detect azole-resistant *A. fumigatus* genotypes in a single culture	Reference MIC testing of multiple colonies (up to 5 colonies)	B	III	Multiple genotypes, i.e. azole-susceptible and azole-resistant, may be present	[115, 492, 493]
		Routine azole agar screening (up to 5 colonies)	B	III	One resistant colony can be identified among 4 susceptible samples together as recently validated.	[118, 491]
	Confirm or reject azole resistance by a validated method	MIC test using EUCAST method and EUCAST BPs (S, I, R)	A	III	Applicable to all *Aspergillus* spp. Breakpoints established for most species	[494-496]

		MIC test using CLSI method and CLSI ECVs (wild-type/non-wild-type)	B	III	Breakpoints not established	[496]
	MIC testing of various *Aspergillus* spp.	Etest®	C	III	Confirmation by reference test recommended.	[497-501]

718 SoR, Strength of recommendation; QoE, Quality of evidence; MIC, minimum inhibitory concentration

719 **Table 17. Azole MIC testing: Choice of azole compounds**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	To determine susceptibility to itraconazole	MIC (EUCAST/CLSI)	A	III	In general, a sensitive marker for azole resistance in *Aspergillus; t*est itraconazole and voriconazole as a minimum	[495, 496, 502-506]
Any	To determine susceptibility to voriconazole	MIC (EUCAST/CLSI)	A	III	Resistance/reduced susceptibility to other azole(s) may accompany that of voriconazole; isolated voriconazole resistance described related to TR_{46} mutation	[114, 494, 496, 504-507]
Any	To determine susceptibility to posaconazole	MIC (EUCAST/CLSI)	B	III	Posaconazole resistance without itraconazole resistance not reported so far; current EUCAST breakpoint will misclassify approximately 15% susceptible isolates as I/R	[300, 486, 495, 496, 504-509]
Any	To determine susceptibility to isavuconazole	MIC (EUCAST/CLSI)	A	III	MIC often similar to voriconazole, but needs testing separately, if isavuconazole is to be used; lower MIC of isavuconazole as compared	[495, 504, 505, 507, 510-512]

					to itraconazole and voriconazole for *A. lentulus* and *A. udagawae* (*A. fumigatus* complex) (CLSI)	

720 SoR, Strength of recommendation; QoE, Quality of evidence; MIC, minimum inhibitory concentration; EUCAST, European Committee on Antimicrobial

721 Susceptibility Testing; CLSI, Clinical & Laboratory Standards Institute

722

723 **Table 18. Amphotericin B susceptibility testing**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Clinically relevant isolate	Confirm or reject AmB resistance when antifungal treatment is considered	MIC test	C	III	Acquired resistance to amphotericin B is very rare and therefore correlation with clinical outcome has not been documented apart from the poorer outcome for high MIC species (*A. terreus* and *A. flavus* compared to *A. fumigatus)*.	[513-516]
Clinically relevant isolate	Interpretation of MIC (EUCAST)	MIC test using EUCAST method and EUCAST break points (S, I, R)	B	III	MIC break points proposed for *A. fumigatus* and *A. niger* Epidemiologic cut-offs established for *A. flavus*, *A. fumigatus*, *A. niger* and *A. terreus* *A. terreus* is not considered a good target for AmB. *A. flavus* may be in vitro resistant	[495, 517, 518]
Clinically relevant isolate	Interpretation of MIC (CLSI)	MIC test using CLSI method and CLSI ECVs (wild-type/non-wild-type)	B	III	ECVs proposed for *A. fumigatus*, *A. flavus*, *A. nidulans*, *A. niger*, *A. terreus*, *A. versicolor.* No clinical break points. *A. terreus* and *flavus*, e.g. with MIC below the ECV are not good targets for AmB. No clinical data that *A. fumigatus* with MIC 2	[519]

					will respond to AmB although classified as wildtype according to CLSI ECVs.	

724 SoR, Strength of recommendation; QoE, Quality of evidence; AmB, amphotericin B; CLSI, Clinical & Laboratory Standards Institute; ECV, epidemiological cut-

725 off value; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibitory concentration

726

727 **Table 19. Antifungal regimens in intrinsic resistance**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Amphotericin B MIC ≥1 mg/L	To cure IA	Replace AmB with azole, if azole tested susceptible	B	II		[17, 170, 520-525]
IA due to *A. terreus*	To cure IA	Voriconazole	A	II	Avoid AmB	[162, 526, 527]
		Isavuconazole	A	II		
		Posaconazole	B	III		
		Itraconazole	B	III		
IA due to *A. calidoustus*	To cure IA	Lipid formulation of AmB	A	II	Avoid azoles	[103, 528]
IA due to *A. tubingensis* (*A. niger* complex)	To cure IA	Other than azole monotherapy	C	III	Higher azole MIC common, but no data on clinical impact	[501, 529, 530]
IA due to *A. lentulus* (*A. fumigatus* complex)	To cure IA	Other than azole monotherapy				
IA due to *A. alliaceus* (*A. flavus* complex)	To cure IA	Other than AmB monotherapy	C	III	Avoid AmB	[531]

IA due to *A. niger* complex	To cure IA	Other than itraconazole and isavuconazole	B	III	Isavuconazole, posaconazole, and voriconazole MIC in general 1 dilution higher compared to *A. fumigatus*; itraconazole MIC in general 2 steps higher; limited clinical data	[501, 512]
IA due to *A. nidulans*	To cure IA	Voriconazole	C	III	AmB MIC elevated, poor clinical responses in chronic granulomatous disease	[532, 533]

728 SoR, Strength of recommendation; QoE, Quality of evidence; AmB, amphotericin B; IA, invasive aspergillosis; MIC, minimum inhibitory concentration

729 **Table 20. Optimal therapy in documented azole-resistance**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Isolate with voriconazole MIC =2 mg/ml	To cure IA	Voriconazole + echinocandin combination therapy or L-AmB monotherapy for IA (as well as for CPA)	A	III	The probability of voriconazole treatment failure may be higher than in voriconazole MIC <2.	[534-536]
Isolate with posaconazole MIC >0.5 mg/ml [537]	To cure IA	L-AmB	A	II_u		[113, 114, 538]
		AmB lipid complex	C	III		No reference found.
		Voriconazole & anidulafungin	B	III		[534]
		Posaconazole & caspofungin	C	III	Posaconazole not licensed for primary treatment	[539]
		Caspofungin or micafungin	C	III	Patients with contra-indications to AmB & other azoles	No reference found.

730 SoR, Strength of recommendation; QoE, Quality of evidence; AmB, Amphotericin B; CPA, chronic pulmonary aspergillosis; IA, invasive aspergillosis; L-AmB,

731 Liposomal amphotericin B; MIC, minimum inhibitory concentration

732 **Table 21. Therapeutic drug monitoring**

Clinical scenarios where antifungal therapeutic drug monitoring may be indicated	**Examples, comments**
Populations with increased pharmacokinetic variability	Impaired gastrointestinal function; hepatic dysfunction; children, elderly patients, obese patients, critically-ill patients
Changing pharmacokinetics	Intravenous to oral switch, changing gastrointestinal function, changing hepatic or function, physiological-instability
Interacting medications	Patient receiving medication known to induce cytochrome P450 enzymes especially CYP3A4, antacids, proton-pump inhibitors (itraconazole capsules, posaconazole suspension), antiretroviral medications. Patients should have medication records screened using drug interactions screening database before starting and stopping antifungals (example: www.fungalpharmacology.org, fungal-druginteractions.org, or http://www.aspergillus.org.uk/content/antifungal-drug-interactions)
Poor prognosis disease	Extensive or bulky infection, lesions contiguous with critical structures, CNS infection, multifocal or disseminated infection
Compliance concerns	Important issue with longer-term consolidation therapy or secondary prophylaxis in outpatient setting

Suspected breakthrough infection	TDM can establish whether fungal disease progression occurred in the setting of adequate antifungal exposure
Suspected drug toxicity, especially neurotoxicity (voriconazole)	Exposure-response relationships are described for other toxicities (e.g., hepatotoxicity), the utility of TDM to prevent their occurrence is less well established

733 CNS, central nervous system; TDM, therapeutic drug monitoring

734

735 **Table 22. Itraconazole therapeutic drug monitoring**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
All patients receiving itraconazoletreatment for IA	Improve efficacy	Measure serum trough level on day 5 of therapy or soon after	A	II	Target itraconazole level >1 mg/L to 4 mg/L by HPLC. Hydroxy-itraconazole metabolite concentrations generally reported separately by HPLC or LC/MS/MS methods, but included in "itraconazole" concentration report by bioassay. Therapeutic range by bioassay may vary by laboratory but typically fall in the range of (3-17 mg/L)	[122, 127, 540-542]
All patients receiving itraconazole for prophylaxis for IA	Improve efficacy	Measure serum trough level on day 5 of therapy or soon after	A	II	Target itraconazole level >0.5 mg/L (HPLC) or > 3 mg/L (bioassay)	[124]
Patients receiving itraconazole	Reduce toxicity	Measure serum trough level on day 5 of therapy or soon after	B	II	Toxicity was associated with itraconazole levels >17.1 mg/L by itraconazole bioassay, which correspond to ~4 mg/L by HPLC	[127]

736 SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; HPLC, high performance liquid chromatography; LC, liquid

737 chromatography; MS, mass spectrometry

738 **Table 23. Voriconazole therapeutic drug monitoring**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
All patients receiving voriconazole treatment for IA	Improve efficacy, safety and compliance	Measure plasma trough level after 2-5 days of therapy or soon after	A	II	Target range of 1-5.5 mg/L	[128-131, 133, 543-545]
		Repeat plasma trough level	B	II	Repeat during second week of therapy, additional samples as clinically indicated and outlined in the text	[128-131, 133, 543-545]
All patients receiving voriconazole prophylaxis for IA	Improve efficacy, safety and compliance of prophylaxis	Measure serum trough level after 2-5 days of therapy or soon after, and 4 days after change of dose	A	IIt	As above; most studies investigated voriconazole treatment rather than prophylaxis	[132, 546, 547]
Patients with IA due to *Aspergillus* strains of reduced azole	Improve efficacy of treatment for isolates with MIC=2 mg/ml	Measure serum trough level after 2 to 5 days of therapy or soon after and 4 days after change of dose	A	II	Trough >2 mg/L recommended on the basis of PK/PD analysis	[131, 548]

susceptibility MIC =2 mg/ml						

SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; MIC, minimum inhibitory concentration; PK, pharmacokinetic; PD, pharmacodynamic

741 **Table 24. Posaconazole therapeutic drug monitoring**

Population	Intention	Intervention	SoR	QoE	Comments	Ref.
Patients receiving posaconazole suspension for **treatment of IA**	Improve efficacy, compliance	Serum trough level on day 5 of therapy or soon after	A	II	Target level >1 mg/L. Gastroresistant tablet or intravenous formulation preferred for most patients, consider switch to tablet or IV, if no therapeutic levels with oral suspension Repeat determination as clinically appropriate Longed half-life gives similar results for random sampling and true trough samples	[138]
Patients receiving posaconazole suspension for **prophylaxis to prevent IA**	Improve efficacy, compliance	Serum trough level on day 5 of therapy or soon after.	C	II	Target level >0.7 mg/L Adequate tissue concentrations may occur despite serum concentration <0.7 mg/L Repeat determination as clinically appropriate	[136, 137, 549-552]

Patients receiving posaconazole	Improve safety	Measure serum trough level on day 5 of therapy or soon after	C	III	If treatment failure or toxicity suspected, TDM may be indicated in patients receiving gastroresistant tablet or intravenous formulation Posaconazole exposures between 0.5-3.75 mg/L are well studied and considered safe and effective with all three formulations Posaconazole plasma levels above this exposure range may be associated with toxicity	[120,121]

742 SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; IV, intravenous; TDM, therapeutic drug monitoring; AML, acute

743 myeloid leukaemia; HSCT, haematopoietic stem cell transplantation; GvHD, graft versus host disease

744

745 **Table 25. Isavuconazole therapeutic drug monitoring**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
All patients receiving isavuconazole	Improve efficacy safety and compliance	Measure serum trough level on D5 of therapy or soon after	C	III	Limited data to support routine TDM but may be indicated in the setting of treatment failure, drug interactions, or if toxicity is suspected The long half-life of isavuconazole (130 hours) may support use for TDM in some clinical situations to confirm drug clearance prior to starting medications metabolized by CYP3A4, especially chemotherapy agents	FDA advisory briefing documents

746 SoR, Strength of recommendation; QoE, Quality of evidence; TDM, therapeutic drug monitoring; FDA, Food and Drug Administration

747 **Table 26. Primary prophylaxis**

Population	Intention	Intervention	SoR	QoE	Comment	Ref
Haematological malignancies, e.g. AML with prolonged and profound neutropenia	Lower incidence of IA	Posaconazole 200 mg tid suspension or 300 mg tablet qd	A	I	AML/MDS induction only. TDM especially with oral suspension. Tablets more bioavailable, bridging with posaconazole IV formulation possible	[553]
		L-AmB 12.5 mg biw, nebulized, with undetermined dose of fluconazole	B	I	AML	[554, 555]
		ABLC 3 mg/kg 3x/weekly	C	II_h	No difference to L-AmB regimen	[556]
		Micafungin 50 mg qd	C	II_t		[560, 561]
		L-AmB 10 mg/kg q7d	C	II_u		[562]
		L-AmB 50 mg abs q2d	C	II_u		[563]
		L-AmB 15 mg/kg q14d	C	II_u		[564]
		Voriconazole	C	II_t	Not better than fluconazole	[565]

		Itraconazole 400 mg/d, oral solution	D	II	No difference to fluconazole (n=195) and more toxicity	[121, 557-559]
Acute lymphoblastic leukaemia, remission induction chemotherapy	Lower incidence of IA	L-AmB 5 mg/kg biw	D	I	L-AmB more toxic than placebo, no significant reduction in IA rate	[566]
Autologous HSCT or treatment of haematological malignancies besides acute leukaemia	Lower incidence of IA	Any mould active agent	D	III		No reference found.
Allogeneic HSCT (until neutrophil recovery)	Lower incidence of IA	Posaconazole 200 mg tid suspension or 300 mg tablet qd	B	II_t	Neutropenia duration approximately identical, TDM*	[553]
		L-AmB 12.5 mg biw, nebulized, with fluconazole	B	II_t		[554]
		Voriconazole 200 mg bid	C	I	Not better than fluconazole, TDM	[567, 568]

		Micafungin 50 mg/d	C	I	But no difference in subgroup analysis for aspergillosis	[560]
		Itraconazole 400 mg/d oral solution	D	I	Toxicity issues; TDM	[554, 559]
Allogeneic HSCT (after neutrophil recovery and no GvHD)		Any antifungal agent	D	III	No study demonstrated outcome advantage	
Allogeneic HSCT (with moderate to severe GvHD and/or intensified immuno-suppression)		Posaconazole 200 mg tid suspension or 300 mg tablet qd	A	I	TDM	[569]
		Voriconazole 200 mg bid	C	II	Not better than fluconazole; TDM	[567, 568]
		Itraconazole 400 mg/d, oral solution	C	II	Toxicity issues; TDM	[559]
		Micafungin 50 mg/d	C	III	Only few patients with GVHD	[560]
Allogeneic HSCT (until neutrophil recovery)	To reduce IA attributable mortality	Posaconazole 200 mg tid suspension or 300 mg tablet qd	B	II_t	Neutropenia duration approximately identical. TDM	[553]
Allogeneic HSCT (after neutrophil recovery, without GvHD)		Any other antifungal	D	III	No study demonstrated outcome advantage	

Allogeneic HSCT (with moderate to severe GvHD and/or intensified immuno-suppression)		Posaconazole 200 mg tid suspension or 300 mg tablet qd	A	II	Mainly IFD-attributable mortality, TDM	[569]

748 SoR, Strength of recommendation; QoE, Quality of evidence; qd, once daily; bid, twice daily; tid, thrice daily; AML, acute myeloid leukaemia; MDS,
749 myelodysplastic syndrome; TDM, therapeutic drug monitoring; ABLC, amphotericin B lipid complex; L-AmB, Liposomal amphotericin B; HSCT,
750 haematopoietic stem cell transplantation; GvHD, graft versus host disease; IFD, invasive fungal disease
751

752 **Table 27. Targeted therapy of pulmonary disease – First line**

Population	Intention	Intervention	SoR	QoE[1]	QoE[2]	QoE[3]	Comment	Ref.
[1] Neutropenia (non- allo HSCT recipients) [2] Allo-HSCT (during neutropenia) [3] Allo-HSCT (w/o neutropenia) or other non-	To increase response and survival rate	Isavuconazole 200 mg iv tid day 1-2, then 200 mg qd oral	A	I	II_t	II_t	D III, if mould active azole prophylaxis less adverse effects than voriconazole	[173, 512, 633, 634]
		Voriconazole 2x 6 mg/kg IV (oral 400 mg bid) on day 1, then 2x 4 mg/kg IV (oral 200 to 300 mg bid)	A	I	II_t	II_t	C III for start with oral; D III, if prior mould active azole prophylaxis; TDM	[170, 172, 512, 635]
		L-AmB 3 mg/kg	B	II	II_t	II_t		[171]
		Combination of voriconazole 6/4 mg/kg bid (after one week oral possible (300 mg bid)) + anidulafungin 200/100 mg	C	I	$II_{t,}$	$II_{t,}$	No significant difference compared to voriconazole, in GM positive (subgroup) better survival; TDM	[172, 635]
		Caspofungin 70 mg qd day 1, followed by 50 mg qd (if body weight <80kg)	C	II	II	II		[618-620]

neutropenic patients		Itraconazole 200 mg q12h iv on day 1, then 200 mg/qd	C	III	$II_{t,a}$	$II_{t,a}$	D III for start with oral, TDM D III, if mould active azole prophylaxis	[512, 542]
		AmB lipid complex (ABLC) 5 mg/kg	C	III	III	III		[636]
		Micafungin 100 mg	C	III	III	III		[637-639]
		AmB colloidal dispersion (ABCD) 4-6 mg/kg	D	I	II_t	II_t		[142]
		Conventional AmB 1-1.5 mg/kg	D	I	II_t	II_t		[170]
		Other combinations	D	III	III	III	Efficacy unproven	[640]
Life-threatening haemoptysis	Bridging until neutrophil recovery	Arterial embolization, emergency surgical intervention	B	III	III	III		[641]

753 SoR, Strength of recommendation; QoE, Quality of evidence; allo-HSCT, allogeneic haematopoietic stem cell transplantation; bid, twice daily; tid, thrice

754 daily, qd, once daily; IA, invasive aspergillosis; IV, intravenous; TDM, therapeutic drug monitoring; GM, galactomannan

755 **Table 28. Targeted therapy of extrapulmonary disease – First line**

Population	Intention	Intervention	SoR	QoE	Comment	Ref
Suspected or proven IA of the central nervous system	To increase response and survival rate	Surgical debridement, if surgically possible	A	II_u		[642, 643]
		Voriconazole	A	II_u	N=5/5	[170]
					N=81, 48 proven cases, 33 probable cases, TDM recommended targeting trough concentration of 2-5.5 mg/L	[642]
		Posaconazole	D	III	8 patients documented in studies (5 failures)	[644]
		Itraconazole	D	III		
		Lipid formulations of AmB	B	III	Case collections, animal data	[645-647]
		cAmB	D	I	Renal toxicity	[189, 648-650]
		Echinocandins	D	III	Insufficient tissue penetration	[646]

Patients with clinical suspicion of or proven invasive sinus aspergillosis	To cure	Surgery	A	III	Need to be considered on an individual basis and decision	
		Local antifungal therapy	C	III		
Patients with invasive sinus aspergillosis (all levels of certainty: suspected through proven)		Voriconazole	A	II_t	N=8/7, TDM recommended	[170, 651]
		L-AmB	A	II_t	Active against mucormycosis as well since mixed infections occur or cannot be differentiated	[171]
		Posaconazole, itraconazole, echinocandins	C	III	Not well specified in studies, TDM recommended for posaconazole and itraconazole	[652, 653]

SoR, Strength of recommendation; QoE, Quality of evidence; TDM, therapeutic drug monitoring; AmB, Amphotericin B, cAmB, conventional amphotericin B; L-AmB, liposomal amphotericin B

759 **Table 29. Fever-driven ("empiric") approach**

Population	Intention	Intervention	SoR	QoE	Comment	Ref
Chemotherapy for haematological malignancies or HSCT, neutropenia <500/µL ≥ 96 h, fever (>38˚C), and parenteral broad spectrum antibacterial therapy ≥ 96 h (some centres consider 48h)	Reduction in the incidence of IA and/or related mortality	Caspofungin 70 mg qd day 1, followed by 50 mg qd (if body weight <80kg)	A	I	Caspofungin was associated with a significantly higher rate of survival than L-AmB (subgroup analysis).	[188]
		L-AmB 3 mg/kg	B	I	Less toxicity in comparison to cAmB but more renal toxicity compared to echinocandin	[188, 189]
		Voriconazole 6 mg/kg bid IV (oral 400 mg bid) on day 1, then 4 mg/kg bid IV (oral 200 to 300 mg bid)	B	II	Failed the 10% non-inferiority cut-off when compared with L-AmB, but first-line for aspergillosis. Activity of azoles empirical therapy for persistent fever may be limited in patients receiving prophylaxis with an agent of the same class. TDM*	[190]
		Itraconazole 200 mg qd iv	C	II	Activity of azoles empirical therapy for persistent fever may be limited in patients receiving prophylaxis with an agent of the same class. TDM*	[666]
		ABLC 5 mg/kg qd	C	I	Infusion-related toxicity (fever, chills, hypoxia)	[667]

		ABCD 4 mg/kg	C	I	Same as above	[668]
		cAmB 0.5-1 mg/kg qd	D	I	Poor tolerance due to extreme toxicity	[189, 342, 649, 650, 666, 668]
		Micafungin 100 mg qd	B	II		[669]
		Fluconazole	D	II_r	No activity against Aspergillus	[670]

SoR, Strength of recommendation; QoE, Quality of evidence; L-AmB, liposomal amphotericin B; cAmB, conventional amphotericin B; IV, intravenous; TDM, therapeutic drug monitoring; ABLC, amphotericin B lipid complex; ABCD, amphotericin B colloidal dispersion

762 **Table 30. Non-haematological patients at high risk**

Population	Intention	Intervention	SoR	QoE	Ref.
SOT lung with pre-transplantation colonization and *Aspergillus* in intraoperative culture OR CMV disease OR higher donor age OR prolonged ischaemia time OR receiving daclizumab OR bronchial anastomotic ischemia OR bronchial stent OR single lung SOT	To identify patients with high risk of IA	Consider prophylaxis	B	III	[210, 226, 692] [215, 693-695]
SOT lung with repeated acute and chronic rejection			B	II_t	[696, 697]
SOT heart with re-operation, CMV infection, haemodialysis, other episode of IA in the program within 2 months	To identify patients with high risk of IA	Consider prophylaxis	A	II_h	[204]
SOT heart with airborne *Aspergillus* spores in ICU			A	II	[203, 204]
SOT heart with sirolimus OR tacrolimus OR hypogammaglobulinemia			B	II_h	[212, 698]
SOT liver with one of the following characteristics: requirement for dialysis OR retransplantation OR fulminant hepatic failure OR MELD score >30	To identify patients with high risk of IA	Consider prophylaxis	B	II_h	[210, 211, 217, 224, 308, 311, 607, 699-702]

SOT liver with one of the following characteristics: ICU admission or corticosteroid requirement previous 2-4 weeks to transplant OR >15 units of packed red blood cells during transplant surgery OR reoperation involving the intraabdominal cavity OR choledochojejunostomy			C	III	
SOT kidney with one of the following characteristics: Pre-transplant COPD OR delayed graft function OR post-transplant blood stream infection OR acute graft rejection	To identify patients with high risk of IA	Consider prophylaxis	A	II_h	[228]
COPD with one of the following characteristics: high (systemic) cumulative glucocorticosteroid dose OR refractory to antibiotic therapy OR admission to the intensive-care unit	To identify patients with high risk of IA	Consider prophylaxis	A	II_t	[232, 257, 703, 704]
HIV with CD4 count <100 cells/µl	To identify patients with high risk of IA	Consider prophylaxis	A	II_h	[232]
ICU patients with either COPD OR requiring glucocorticosteroids therapy	To identify patients with high risk of IA	Consider prophylaxis	A	II_h	[257, 703, 704]
ICU patients with either acute liver failure OR burns OR severe bacterial infection OR malnutrition			B	III	

ICU or SOT recipients with Increased environmental exposure	To identify patients with high risk of IA	Consider prophylaxis	A	II	[203, 204, 705, 706]
Liver insufficiency	To identify patients with high risk of IA	Consider prophylaxis	B	II_h	[244, 707]
Burn patients with positive fungal cultures	To identify patients with high risk of IA	Consider prophylaxis	A	II_h	[708, 709]
Percentage of total body surface area burn injury; length of stay			B	III	[706]
Patient receiving one of the following: TNF-α blockers, basiliximab, daclizumab, infliximab, etanercept, alemtuzumab, adalimumab, rituximab, abatacept	To identify populations at high risk of IA	Consider prophylaxis	C	III	No reference found.

763 SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; CMV, cytomegalovirus; ICU, intensive care unit; COPD, chronic

764 obstructive pulmonary disease; BAL, bronchoalveolar lavage

765

766 **Table 31. Diagnosis-driven ("pre-emptive") approach in non-haematological patients**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
COPD	To diagnose IA	Respiratory culture	A	II_u	Isolation of *Aspergillus* in culture from admitted patients with COPD represents IA in at least 22% of patients	[257, 281, 282, 710]
COPD	To diagnose IA	GM BAL	B	II_u	Sensitivity/specificity of BAL GM >1.0 cut-off is 67% / 96%, at GM >0.5 cut-off is 89% / 88%	[281]
Underlying respiratory disease	To diagnose IA	Lateral flow device BAL	C	II	Sensitivity / specificity 77% / 92% (Not commercially available at the time of writing)	[285]
HIV	To diagnose IA	Direct microscopy	A	II_h	50% positive	[232]
HIV	To diagnose IA	GM BAL	B	II_u	53% positive	[232]
HIV	To diagnose IA	GM serum	B	II_u	34% positive	[232]
HIV	To diagnose IA	Histology	A	II_u	75% positive	[232]
ICU	To diagnose IA	BDG serum	B	II_u	Autopsy study, non-haematological immunocompromised critically	[429]

					ill patients with lower respiratory tract infection. Using 140 pg/ml cut-off, sensitivity/specificity 100% / 70%	
ICU	To diagnose IA	BDG serum	B	II_u	BDG appeared a mean of 6.5 days before *Aspergillus* was grown	[711]
ICU	To diagnose IA	Respiratory culture	B	II_u		[89, 712, 713]
ICU	To diagnose IA	GM BAL	C	II_u	Using cut-off ODI 0.5 sensitivity/specificity 88-90% / 87-100%	[89, 712, 713]
ICU	To diagnose IA	SeptiFast®	C	II_h	Sensitivity/specificity 66% / 98%, PPV 93%, NPV 88%	[714, 715]
Non haematological	To diagnose IA	Culture	A	II_h	Very low PPV of *Aspergillus* spp. culture from respiratory samples	[197]
Non haematological	To diagnose IA	Culture	A	II_h	Sensitivity of BAL higher for non-neutropenic patients	[52]
Non-haematological	To diagnose IA	GM serum	C	II	Using cut-off of 0.5 ng/ml sensitivity/specificity 60% / 89%	[710]

Non-haematological	To diagnose IA	MycAssay Aspergillus®	C	II	Sensitivity, specificity, PPV, and NPV of first sample/any sample were 87%/93%, 87%/82%, 34%/34%, 92%/100%	[278]
SOT, any	To diagnose IA	Respiratory culture	D	II	Low sensitivity and specificity	[87, 282]
SOT, any	To diagnose IA	GM BAL	B	II	Using cut-off ODI 1.0 sensitivity/specificity 100% / 91%	[716]
SOT, any	To diagnose IA	High-resolution chest computed tomography	A	III	Bilateral bronchial wall thickening and centrilobular opacities, tree-in-bud pattern (65%), ground-glass opacities and/or bilateral areas of consolidation (23%)	[214, 717]
SOT, any	To diagnose IA	Lateral flow device BAL	C	II	N=11 SOT	[284, 434, 718]
SOT Heart	To diagnose IA	Respiratory culture	A	II_h	Overall positive predictive value (PPV) 60-70%, PPV 88-100% with respiratory specimens other than sputum; recovery of *A. fumigatus* PPV 78-91%	[271]
SOT Heart	To diagnose IA	High-resolution computed tomography	A	II_h	Provided significant additional information in 41%; positive with a normal chest X-ray in 18%	[274]

		of the thorax				
SOT Lung	To diagnose IA	BDG serum	C	II_u	Sensitivity/specificity 64%, 9%, PPV 14%, NPV 50%	[719]
SOT Lung	To diagnose IA	GM BAL	B	II	Using cut-off ODI 1.5 sensitivity/specificity 100% / 90%	[87, 88, 720, 721]
SOT Lung	To diagnose IA	PCR of respiratory samples	B	II		[88]

767 SoR, Strength of recommendation; QoE, Quality of evidence; COPD, chronic obstructive pulmonary disease; BDG, ß-D-glucan; IA, invasive aspergillosis; ICU,
768 intensive care unit; SOT, solid organ transplantation; PPV, positive predictive value; GM, galactomannan; ODI, optical density index; NPV, negative predictive
769 value; BAL, bronchoalveolar lavage; PCR, polymerase chain reaction

770 **Table 32. Treatment in non-haematological patients**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
HIV	To treat IA	Voriconazole	A	III	Consider drug-drug interactions with antiretroviral drugs.	[722]
SOT Heart	To treat IA	Itraconazole	C	III	6 patients cured with itraconazole 200-400 mg/d Erratic absorption and interaction with calcineurin inhibitors and other agents	[723]
SOT, any	To treat IA	Voriconazole	A	III	e.g. Herbrecht study 11 SOT; voriconazole increases the levels of anti-calcineurin immunesuppressors, TDM; monitor liver function tests especially in liver transplant recipients.	[170, 214, 287, 333, 607-609, 673, 724-726]
SOT, any	To treat IA	L-AmB	A	II		[678, 727, 728]
SOT, any	To treat IA	Voriconazole &	B	II	40 SOT voriconazole & caspofungin (n=40) vs amphotericin B (n=47).	[289]

		caspofungin			Survival benefit in pts with *A. fumigatus* or renal insufficiency	
SOT, if voriconazole contraindicated	To treat IA	Caspofungin	B	III	Complete response 83%; response 7/9 monotherapy and 7/10 combination	[621, 622, 686, 729]

771 SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; SOT, solid organ transplantation; L-AmB, Liposomal amphotericin B; SOT,

772 solid organ transplantation; TDM, therapeutic drug monitoring

773

774 **Table 33. Prophylaxis in non-haematological patients**

Population	Intervention	Intention	SoR	QoE	Comment	Reference
SOT Lung	Universal* prophylaxis	To prevent IA	A	I	Invasive fungal infection appeared at a median of 35 days	[304, 315, 730]
	Targeted* prophylaxis	To prevent IA	C	III		[315, 694, 731]
	Inhaled cAmB	To prevent IA	B	II_h	25 mg/day for 4 days, followed by 25 mg/week for 7 weeks. More adverse events in inhaled deoxycholate vs lipid-based Breakthrough IA in 7-10%	[732, 733]
	Inhaled lipid-based AmB	To prevent IA	A	I	More adverse events with inhaled deoxycholate vs lipid-based but similar efficacy; various possible protocols: 50mg/day for 4 days, then 50mg/week for 7 weeks; 50mg/day for 2 weeks, then once weekly for 10 weeks; 25mg thrice weekly between day 1 and day 60 post SOT and once weekly between day 60 and day 180	[724, 732-735]

	Voriconazole	To prevent IA	A	III	Voriconazole 2x200 mg/d more hepatotoxic than itraconazole 2x200 mg/d. Usual duration of prophylaxis 3-6 months; monitor liver and skin toxicity	[303, 304, 315, 731, 736]
	Voriconazole pre-emptive, if colonized	To prevent IA	B	II_u	Breakthrough IA <2% at 6 months	[731]
	Voriconazole for three months	To prevent IA	C	II	No effect of voriconazole on the incidence of IA (45% vs 49%)	[303]
SOT Heart	Universal* prophylaxis with itraconazole or inhaled AmB	To prevent IA	C	I		[214, 737, 738]
	Universal* prophylaxis with itraconazole or inhaled AmB	To prevent IA	C	II	IA rates 5% without prophylaxis, 1.5% with itraconazole 2x200 mg, 0% with inhaled AmB	[214, 737, 738]
	Targeted* prophylaxis with echinocandins	To prevent IA	A	II_t	Prophylaxis in 10% of patients, IA rate reduced from 9% to 2%, attributable mortality from 6% to 2%; duration dependant of risk	[215]

					factors persistence	
SOT Liver	Targeted* prophylaxis with lipid AmB	To prevent IA	B	III	IA rate reduced, mortality unaffected	[607, 739-741]
	Targeted* prophylaxis with echinocandins	To prevent IA	A	I	Standard dosed echinocandins reduced IA rate; duration of prophylaxis usually 21 days post SOT	[217, 308, 311, 742]

775 SoR, Strength of recommendation; QoE, Quality of evidence; * targeted prophylaxis = only if additional risk factors; universal prophylaxis = to all patients in
776 population; IA, invasive aspergillosis; SOT, solid organ transplantation; AmB, Amphotericin B; cAmB, conventional amphotericin B deoxycholate
777

778 **Table 34. Prophylaxis in children at high risk**

Population	Intention	Intervention	SoR	QoE	Comment	Ref
Allogeneic HSCT, pre-engraftment phase; Allogeneic HSCT, post-engraftment phase, GvHD and augmented immunosuppression; High-risk patients with de novo or recurrent leukaemia, bone marrow failure syndromes with prolonged and profound neutropenia	Prevention of IA	Itraconazole	A/B*	II_t	TDM recommended; Approved indication; not approved EU < 18 years	[122, 559, 570-579]
		Posaconazole	A	II_t	TDM recommended; only supportive paediatric data for ≥ 13 years of age	[136, 137, 338, 553, 569, 580-586]
		Voriconazole	A	II_t	Not approved for <2 years; Inference from efficacy from HSCT trials and supportive studies; TDM recommended	[130, 131, 135, 546, 567, 568, 587-593]
		Liposomal amphotericin B	B	II_t/III*	Not approved for prophylaxis; Optimal dose of alternate administration unknown; Alternative if triazoles are not tolerated / contraindicated	[563, 594-599]

		Micafungin	B	II_t/III*	No definite evidence (trend only) for prophylactic efficacy against *Aspergillus* spp. Alternative if triazoles are not tolerated or contraindicated	[560, 600-604]
Chronic granulomatous disease (CGD) patients	Prevention of IA	Itraconazole	A	II	Approved indication; not approved in the EU for < 18 years; TDM recommended	[122, 575-578, 605, 606]
		Posaconazole	A	III	Not EU approved for children < 18 years; TDM recommended; PK and safety data for children ≥ 4 years	[136, 137, 582-585]

* SoR = B for allogeneic HSCT post-engraftment phase, GvHD (graft versus host disease) and augmented immunosuppression

* QoE = III for allogeneic HSCT post-engraftment phase, GvHD and augmented immunosuppression

SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; TDM, therapeutic drug monitoring; HSCT, haematopoietic stem cell transplantation

784 **Table 35. Treatment in children**

Population	Intention	Intervention	SoR	QoE	Comment	Ref
Any paediatric population other than neonates	Treatment proven/probable IA	Voriconazole 18 mg/kg/d iv day 1, followed by 16 mg/kg/d iv or 18 mg/kg/d po in 2 divided dosages (up to 14 years and < 50 kg); if >15 yrs or >12 yrs and >50 kg use adult dosing recommendations	A	II_t	Not approved in patients <2 yrs; TDM recommended.	[130, 131, 135, 170, 333, 546, 589-592, 607-613]
Any paediatric population other than neonates	Treatment proven/probable IA	L-AmB 3 mg/kg/d	B	II_t	Comparison between 2 dosages of L-AmB, no comparison to voriconazole	[171, 597, 599, 614-617]
Any paediatric population other than neonates	Treatment proven/probable IA	Caspofungin 70 mg/m^2 day 1, followed by 50 mg/m^2/d (max. 70 mg/d)	C	II_t	Study prematurely stopped due to low accrual	[616, 618-628]
Neonates	Treatment proven/probable IA	L-AmB 3 mg/kg/d	A	III		[629-632]

785 SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; TDM, therapeutic drug monitoring; L-AmB, liposomal amphotericin B

786 **Table 36. Secondary prophylaxis**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Previous IA and undergoing allogeneic HSCT or entering risk period with non-resectable foci of *Aspergillus* disease	To reduce risk of IA recurrence	Secondary prophylaxis with an *Aspergillus* active antifungal proven to be effective in the actual patient	A	II	Results compared to historical data, mostly in allogeneic HSCT setting	[654-659]
		Voriconazole	A	II_h	IA: 31/45 pts, 1 year cumulative incidence of IFD 6.7±3.6%, TDM	[654]
		Caspofungin 70 mg day 1, followed by 50 mg/d IV until stable engraftment, followed by 400 mg itraconazole suspension PO	B	II_h		[658]
		L-AmB followed by voriconazole	C	II	Fungal infection related mortality 28% despite lipid-based AmB	[657, 660]
Previous IA and with resectable foci of *Aspergillus* disease	To reduce risk of IA recurrence	Surgical resection following by secondary prophylaxis	B	III	Timing and methods of surgery important. Concomitant administration of appropriate antifungal compound justified.	[661-665]

before entering risk period					Indication for surgical intervention by appropriate specialist. Interdisciplinary consensus needed.	

787 SoR, Strength of recommendation; QoE, Quality of evidence; HSCT, haematopoietic stem cell transplantation; IA, invasive aspergillosis, IFD, invasive fungal

788 disease; TDM, therapeutic drug monitoring, PO, per os; L-AmB, liposomal amphotericin B

789 **Table 37. Antifungal drugs in refractory disease**

Population	Intention	Intervention	SoR	QoE	Comment	Ref
Haematological patients with refractory IA	Achieve complete or partial response, or stable disease, improve survival	Switch to another drug class	A	III		
		Any combination	C	III	No prospective study demonstrated superiority of combination therapy over monotherapy	[671]
		Voriconazole	A	II		[333, 672-674]
		L-AmB 3-5 mg/kg	B	II	Majority voted for BII others for AII	[598, 675, 676]
		ABLC 5 mg/kg	C	II		[636, 676-678]
		ABCD			No longer commercially available	[679, 680]
		Caspofungin 70 mg qd day 1, followed by 50 mg qd (if body weight <80kg)	B	II	Very few data in case of voriconazole/posaconazole failure	[335, 674, 681-687]
		Micafungin 75-200 mg qd	C	II		[638, 688]

		Posaconazole 200 mg qid or 400 bid suspension or 300 mg tablet bid day 1, followed by 300 mg qd	B	II		[138, 336, 689, 690]
		Itraconazole	D	III	In case of refractoriness to voriconazole	
		Itraconazole oral forms	C	II	Poor bioavailability	[126]
		Itraconazole IV formulation			Commercially not available everywhere	[542, 691]

790 SoR, Strength of recommendation; QoE, Quality of evidence; L-AmB, Liposomal amphotericin B; ABLC, amphotericin B lipid complex; ABCD, amphotericin B

791 colloidal dispersion; IV, intravenous; TDM, therapeutic drug monitoring; qd, once daily; bid, twice daily; qid, four times daily

792

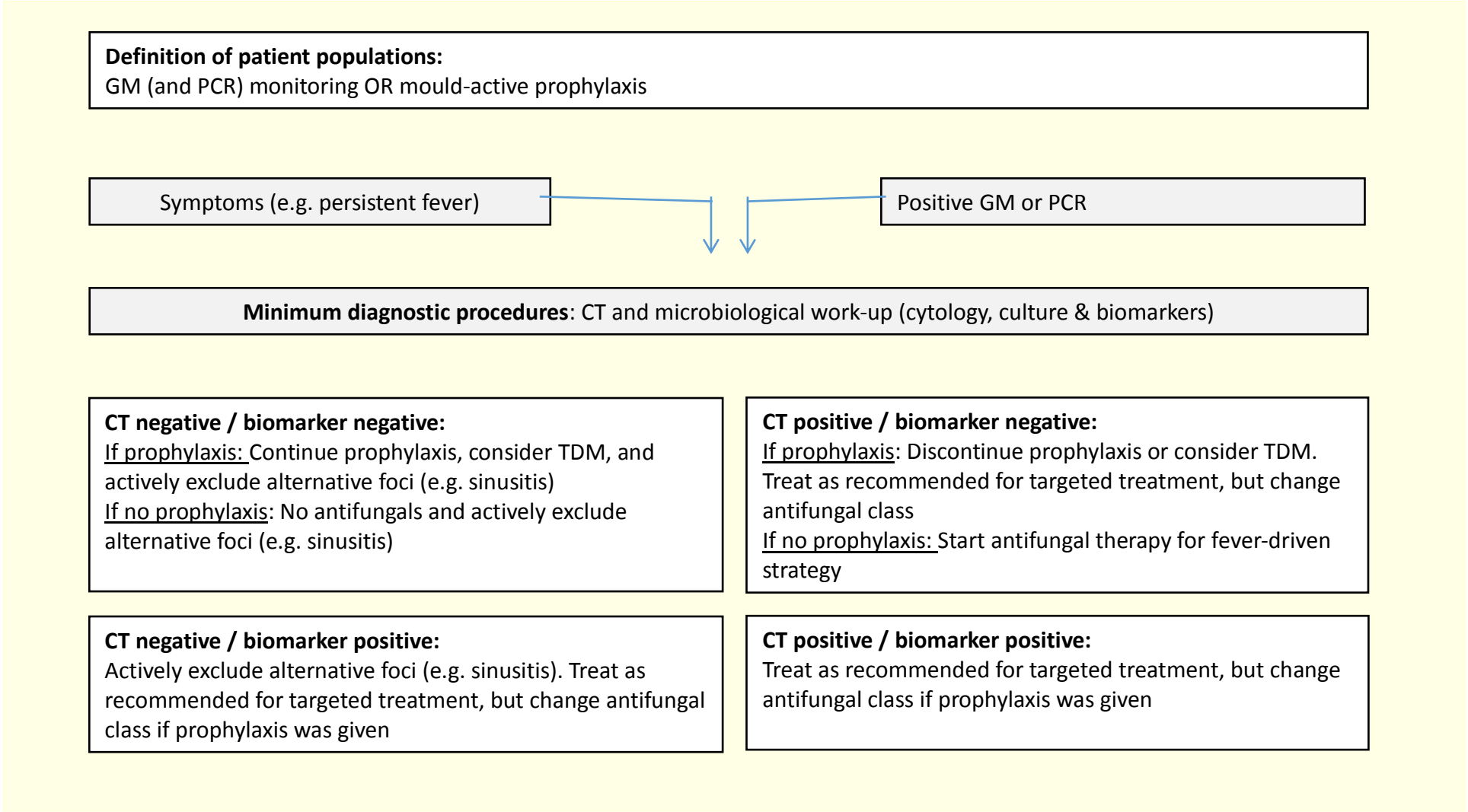
793 **Table 38. Chronic pulmonary aspergillosis**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Cavitary or nodular pulmonary infiltrate in non-immuno-compromised patients	Diagnosis or exclusion of CPA	Direct microscopy for hyphae	A	II_t	Positive microscopy is a strong indicator of infection, not studied in CPA, but in ABPA	[743]
		Histology	A	II	In CPA histology distinguishes between CNPA and CCPA	[744]
		Fungal culture (respiratory secretion)	A	III	Bacterial culture plates are less sensitive than fungal culture plates	[269]
Cavitary or nodular pulmonary infiltrate in non-immuno-compromised patients	Diagnosis or exclusion of CPA	*Aspergillus* IgG antibodies	A	II	IgG and precipitins test standardization incomplete	[364]
CPA patients with progressive disease	Control of infection	Itraconazole: Start 200 mg bid, adjust with TDM	A	II	No data to indicate which agent is preferable	[364, 745]

		Voriconazole Start 150-200 mg bid, adjust with TDM			Voriconazole preferred for CNPA and patients with fungal balls to minimize risk of resistance	[366, 746, 747]
		Posaconazole 400 mg bid (oral suspension) 300 mg qd (delayed release tablets)	B	II	Higher rate of adverse events, if some adverse events with itraconazole and voriconazole	[748]

SoR, Strength of recommendation; QoE, Quality of evidence; CPA, chronic pulmonary aspergillosis; ABPA, allergic bronchopulmonary aspergillosis; SAIA, subacute invasive aspergillosis; CNPA, chronic necrotising pulmonary aspergillosis; CCPA, chronic cavitary pulmonary aspergillosis; qd, once daily; bid, twice daily; TDM, therapeutic drug monitoring

798 **Figure 1. Management during neutropenia**



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